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İÇİNDEKİLER / CONTENTS

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Effect Of Estradiol Progesterone Combination On Pregnancy In IVF-ICSI-ET Cycles

Östrodiol Progesteron Kombinasyonunun İVF – ICSI – ET Sikluslarında Gebe Kalmaya Etkisi

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Abstract

Objective: There are various treatment protocols in which different gonadotropins are used with or without pituitary down-regulation by using gonadotropin-releasing hormone (GnRH) agonists or antagonists. Since no single protocol suits every patient, the treatments should be individualized. Within the scope of this research, we aimed to elucidate the pregnancy rates achieved with progesterone and progesterone estradiol (E2) combination for luteal phase (LP) support in ICSI – ET cycles with ovarian hyperstimulation using GnRH analog were compared.
Method: This study evaluated 142 infertile couples aged between 20 and 40. The patients' admission histories and physical and pelvic examination findings were recorded. Basal serum FSH, LH, E2, prolactin, TSH, and free T3 – T4 levels were measured in each patient on the second or third day of the cycle. A long protocol with GnRH agonist was applied to all patients.
Results: Of the 142 patients in the study, 71 were randomized (1:1) to receive vaginally gel progesterone and transdermal estrogen for luteal phase support, and 71 to receive gel progesterone vaginally. When the cycles with and without pregnancy were evaluated independently of the groups, a significant difference was found in terms of female age, male age, and mean gonadotropin amounts used ($p<0.05$). When the E2 measurements in the group with and without a pregnancy were examined, no significant difference was found in the basal E2 level, the E2 level on the hCG day, and the early luteal phase, that is, on the day of embryo transfer ($p=0.788$, $p=0.735$ and $p=0.474$, respectively). However, E2 levels were higher in pregnant women.
Conclusion: In conclusion, data showing the superiority of one gonadotropin option over another in IVF/ICSI treatment cycles are insufficient. The choice of gonadotropin in controlled ovarian stimulation depends on the product's availability and should be based on ease of use and cost.

Keywords: Infertility, Pregnancy, In-Vitro Fertilization, Embryo Transfer, Luteal Phase.

Özet

Amaç: Gonadotropin salgılatıcı hormon (GnRH) agonistleri veya antagonistleri kullanılarak farklı gonadotropinlerin hipofiz down-regülasyonu ile veya olmadan kullanıldığı çeşitli tedavi protokolleri vardır. Her hastaya uyacak tek bir protokol olmadığı için uygulanacak tedaviler kişiye özel olmalıdır. Bu araştırma kapsamında, GnRH analoğu kullanılarak overhiperstimülasyonunun karşılaştırıldığı ICSI – ET sikluslarındaluteal faz (LF) desteği için progesteron ve progesteron estradiol(E2) kombinasyonu ile elde edilen gebelik oranlarının aydınlatılmasını amaçladık.
Yöntem: Bu çalışmada yaşları 20 – 40 arasında değişen 142 infertil çift değerlendirildi. Hastaların başvuru öyküleri, fizik ve pelvik muayene bulguları kaydedildi. Siklusun ikinci veya üçüncü gününde her hastada bazal serum FSH, LH, E2, prolaktin, TSH ve serbest T3 – T4 düzeyleri ölçüldü. Tüm hastalara GnRH agonisti ile uzun protokol uygulandı.
Bulgular: Çalışmadaki 142 hastadan 71'i luteal faz desteği için vajinal jel progesteron ve transdermal östrojen ve 71'i vajinal jel progesteron almak üzere randomize edildi (1:1). Gebelik olan ve olmayan sikluslar gruplardan bağımsız değerlendirildiğinde kadın yaşı, erkek yaşı ve kullanılan ortalama gonadotropin miktarları açısından anlamlı fark bulundu ($p<0.05$). Gebeliği olan ve olmayan grupta E2 ölçümleri incelendiğinde bazal E2 düzeyi,

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hCG günü E2 düzeyi ve embriyo transferi günü olan erken luteal fazda anlamlı fark bulunmadı (sırasıyla p=0.788, p=0.735 ve p=0.474). Bununla birlikte, hamile kadınlarda E2 seviyeleri daha yüksekti.
Sonuç: Sonuç olarak, IVF/ICSI tedavi sikluslarında bir gonadotropin seçeneğinin diğerine üstünlüğünü gösteren veriler yetersizdir. Kontrollü ovaryan stimülasyonda gonadotropin seçimi, ürünün mevcudiyetine bağlıdır ve kullanım kolaylığı ve maliyete dayanmalıdır.

Anahtar Kelimeler: İnfertilite, Gebelik, Tüp Bebek, Embriyo Transferi, Luteal Faz.

INTRODUCTION

Infertility is the inability of a couple of reproductive age to conceive despite at least one year of regular sexual intercourse without using any contraceptive method. Infertility affects 10 – 15% of couples of reproductive age (1). The standard evaluation is the demonstration of ovulation, adequate sperm production, and normal uterine cavity on hysterosalpingography and the demonstration of tubal patency. At the end of the unprotected 12-month period, 80% of the couples can get pregnant within the first six months, and only 10% of the remaining couples can get pregnant within the following six months (2). The prevalence and main causes of infertility, female infertility alone was responsible for one-third of the cases and male infertility alone in one-fifth. In addition, the problem was seen in men and women at a rate of 39% (3).

Ovulation disorders (32%) and tubal damage (26%) were the most common causes of female infertility. The rate of unexplained infertility is approximately 9%. If a cause can be identified, a general course of treatment becomes evident. The ovaries are in constant communication with other endocrine organs. It is undeniable that the uterus is also an endocrine organ. Therefore, it should be considered that an existing endocrine disorder in women may affect fertility to varying degrees (4).

The treatment approach is purely empirical in unexplained infertility since the underlying abnormality causing infertility cannot be revealed. The wait-and-see approach consists of ovulation induction (OI) with oral or injectable drugs, intrauterine insemination (IUI) alone or combined with ovulation induction, and in-vitro fertilization (IVF). It has been reported that the pregnancy rate per cycle is 8.7 – 11.4% with OI and IUI treatment with gonadotropins (5).

The first successful delivery after in-vitro fertilization was achieved by obtaining a single oocyte in a spontaneous ovulatory cycle and performing a single embryo transfer. However, the success rate of this method is low, and clinicians today have adopted ovarian stimulation strategies. that will ensure the synchronous development of many follicles (6). Controlled ovarian stimulation (COS) is the development of a large number of follicles in the same cycle with the aim of obtaining an ideal number and quality of oocytes from the ovaries within the scope of IVF. Increasing oocyte quality and live birth rates improving ovarian response, and reducing the risk of ovarian hyperstimulation in patients with ovarian reserve is the key (7).

There are various treatment protocols in which different gonadotropins are used with or without pituitary down-regulation by using gonadotropin-releasing hormone (GnRH) agonists or antagonists. Since there is no single protocol to suit every patient, the treatments to be applied should be individualized by considering the age of the woman, ovarian reserve, endocrine status, and related conditions such as endometriosis, polycystic ovary syndrome (PCOS) and ovarian cyst (8).

It has been shown that ovarian cysts that develop with GnRH agonists can be effectively prevented in the long protocol in which oral contraceptives (OCs) were added. It is also

known that with the addition of OCs, the pituitary is suppressed for a shorter time. Less gonadotropin is needed without affecting the number of oocytes obtained and pregnancy results. In addition, it is advantageous in that it enables the IVF treatment to be programmed and prevents the unintentional use of GnRH agonists in case of spontaneous pregnancy (9).

Within the scope of this research, we aimed to elucidate the pregnancy rates achieved with progesterone and progesterone estradiol (E2) combination for luteal phase (LP) support in ICSI – ET cycles with ovarian hyperstimulation using GnRH analog were compared.

METHOD

This study evaluated 142 infertile couples aged between 20 and 40. The patients' admission histories and physical and pelvic examination findings were recorded. Basal serum FSH, LH, E2, prolactin, TSH, and free T3 – T4 levels were measured in each patient on the second or third day of the cycle. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution, and informed consent has been obtained from all participants.

Patients with serum FSH levels of 10IU/ml and E2 below 80 pg/ml measured on the second or third day of menstruation were included. Ovarian volume and antral follicle count were determined by transvaginal ultrasonography (USG). The endometrial cavity and tuba were evaluated with hysterosalpingography. IVF – ICSI – ET was prepared considering the malefactor, age factor (38≤), unexplained factors, and tubal factor indications, as the causes of infertility may differ in the patients.

A long protocol with GnRH agonist was applied to all patients. The treatment was initiated subcutaneously with a GnRH analog on the 21st day of the previous cycle. Patients were called on the second or third day of the menstrual cycle to determine whether there was pituitary down regulation. The absence of follicular activity in transvaginal USG and serum E2 below 80 pg/ml were considered down-regulation. Ovulation induction was started with a combination of recombinant FSH (rFSH) or recombinant FSH/human menopausal gonadotropin (rFSH/hMG). In order to prevent premature LH surges, the dose of GnRH analog was reduced by half and continued until the day of hCG. The Gonadotropin dose was determined by the patient's age, weight, basal E2, FSY level, ovarian volume, and previous ovulation induction response, if any.

Oocyte retrieval was performed at 35 – 37 hours from the hCG dose. Patients randomly used vaginal progesterone gel alone or transdermal E2 in addition to progesterone gel. Those who received a combination of progesterone and E2 were called Group 1, and those who received only progesterone were called Group 2. The treatment was initiated on the day of oocyte retrieval and continued according to the β-hCG result. If β-hCG was negative, both treatments were discontinued. If β-hCG was positive, estradiol treatment was discontinued, and progesterone support was continued until the 12th gestational week

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data was given as descriptive values. For comparisons between groups, the “Independent Sample T–test” was used for two groups, and the “Pearson Chi-

Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Of the 142 patients in the study, 71 were randomized (1:1) to receive vaginally gel progesterone and transdermal estrogen for luteal phase support, and 71 to receive gel progesterone vaginally. The malefactor was found in 38% (n=31) of the patients in the first group and 38% (n=27) in the second group. Unexplained infertility was detected in 43.7% (n=27) of the patients in the first group and 53.6% (n=38) in the second group. The tubal factor was observed in 9.9% (n=7) of patients in the first group and 2.8% (n=2) in the second group. Age factor was present in 5.6% (n=4) of the patients in the first group and 2.8% (n=2) in the second group. Both age factor and male factor were determined in 2.8% (n=2) of the patients in the first group and 2.8% (n=2) of the patients in the second group. IVF – ICSI – ET procedure applied (Table 1).

Table 1. Infertility reasons for both treatment groups (Group 1 & Group 2)

	Group 1		Group 2	
	n	**%**	**n**	**%**
Male Factor	27	38	27	38
Unexplainedinfertility	31	43,7	38	53,6
TubalFactor	7	9,9	2	2,8
Age Factor	4	5,6	2	2,8
Age Factor& Male Factor	2	2,8	2	2,8

Recombinant FSH (rFSH) was initiated in 71 patients in the first group. In addition to rFSH, hMG was started in 23 patients in the first group, and rFSH was started in 71 patients in the second group. testicular sperm extraction (TESE) was performed in 25.9% (n=7) of the patients in the first group and 48.1% (n=13) in the second group because of the male factor. There was no significant difference between the two groups in the study regarding female age, male age, and infertility duration (Table 2).

Table 2. The duration of the infertility period, female age, and male age within the study groups

	Group 1	Group 2	p-value
Female Age	30,92±4,77	31,13±4,748	0,792
Male Age	34,28±5,55	35,24±5,25	0,293
InfertilityPeriod	7,24±3,42	7,69±4,25	0,834

Between the two treatment groups, baseline FSH, mean gonadotropin dose, induction time, mature follicle level, E2 level on day hCG, number of oocytes, number of oocytes retrieved, number of fertilized oocytes, number of embryos transferred, endometrial thickness and E2 level on the day of transfer, and E2 levels on the β-hCG day revealed no significance. The basal E2 level (45.74±15.45) in the second group was statistically significantly higher than in the first group (p=0.005).

On the 12th day after embryo transfer, β-hCG positivity was 28.2% (n=20) in the first group and 25.4% (n=18) in the second group. When all patients were evaluated together, β-hCG

positivity was found on Day 12 in 38 (26.8%) of 142 patients, but there was no significant difference between the groups.

Considering the estradiol measurements, no clinically significant difference was found in the measurements on the hCG day, embryo transfer day, and the 12th day of the cycle (p=0.677, p=0.363, and p=0.777, respectively).

When the cycles with and without pregnancy were evaluated independently of the groups, a significant difference was found in terms of female age, male age, and mean gonadotropin amounts used (p<0.05). In the pregnant group, the ages of men and women are younger, and the amount of gonadotropin used is also lower.

When the E2 measurements in the group with and without a midwife were examined, no significant difference was found in the basal E2 level, the E2 level on the hCG day, and the early luteal phase, that is, on the day of embryo transfer (p=0.788, p=0.735 and p=0.474, respectively). However, E2 levels were higher in pregnant women (Table 3).

Table 3. The properties of groups with and without pregnancy

	Pregnancy (n=38)	No Pregnancy (n=104)	p-value
Basal FSH	6,71±1,35	7,13±1,83	0,198
Basal E2	42,84±13,32	42,05±16,09	0,788
Female Age	29,68±4,51	31,51±4,75	0,042
Male Age	33,11±4,58	35,37±5,57	0,027
Gonadotropin usage	1948,68±572,42	2271,59±749,93	0,017

DISCUSSION

The number and quality of oocytes and embryos are important determinants of success in any IVF-ICSI cycle. There are conflicting results in the literature of studies on serum E2 and serum progesterone (P4) values on hCG day, one of the factors affecting this parameter. On the day of human chorionic gonadotropin administration, the higher the E2 value, the higher the E2 value per follicle, oocyte, and M2 oocyte. Many studies state that the high level of E2 on the trigger day does not affect IVF results but has good or bad effects (10). Blazar et al. reported that continuing clinical pregnancy rates increase as serum E2 levels rise on the hCG day until they reach an approximate plateau of 2500 pg/ml. In addition, they also stated that the increase in the number of oocytes collected during ovum pick-up (OPU) is not always correlated with higher pregnancy rates (11).

High serum progesterone value impairs endometrial receptivity. It provides this negative effect through endometrial gene expression. Studies on IVF cycles with different COS protocols have shown that pregnancy rates are lower when the serum P4 value on the hCG day exceeds 1.5 ng/mL, and this has been evaluated in favor of premature luteinization (PL) (12).

There are also meta-analyses on the effect of estrogen supplementation on pregnancy rate. The first meta-analysis on this subject stated that E2 supplementation for luteal support did not positively contribute to pregnancy rates (13). The next meta-analysis on this topic was by Jee et al. in 2010, and similar results were published (14). Oral, transdermal, and vaginal E2 supplementation was evaluated in both agonist and antagonist cycles, and another meta-analysis involving 15 studies and 2.406 patients revealed that E2 supplementation was not significant in all routes of administration (15). However, it was reported that the transdermal

and vaginal routes should be examined better. Again, in a Cochrane review conducted in 2015, it was reported that supplementing the luteal phase with estrogen in addition to progesterone had no effect on pregnancy achievement, ongoing pregnancy, and abortion rates (16). Meta-analyses include agonist and antagonist cycles, and differences in estrogen administration routes and doses are noteworthy. More recent studies have investigated estrogen supplementation in the luteal phase for some specific patient groups, for example, in cases with a thin endometrium (17) and patients with low serum E2 per follicle (18). It has been shown that E2 support has no positive effect in both patient groups. Groups, patient characteristics, and E2 support must be homogenized for the event to become clear.

Many studies and meta-analyses are comparing GnRH agonist and antagonist treatment protocols. In the Cochrane review published in 2001, the newly applied fixed GnRH at that time when the antagonist protocol was compared with the standard GnRH agonist long protocol, a significant decrease was found in the incidence of severe ovarian hyperstimulation syndrome (OHSS), but lower pregnancy rates were reported with the antagonist protocol. However, pregnancy rates were found to be lower when compared to agonists (19). In 2011, a Cochrane meta-analysis comparing GnRH antagonist and agonist protocols reported no difference between the two protocols regarding live birth and ongoing pregnancy rates (20).

The 2016 updated review of this meta-analysis included 73 randomized controlled trials and found no difference in live birth rates (OR 1.02, 95% CI 0.85 to 1.23). On the other hand, the incidence of OHSS of all severity has been reported to be lower in GnRH antagonist protocols (OR 0.61, 95% CI 0.51 to 0.72). However, cycle cancellation due to poor ovarian response was higher in patients receiving GnRH antagonists than those receiving agonists (OR 1.32, 95% CI 1.06 to 1.65) (21). Similarly, Xiao JS et al. compared standard long agonist and antagonist protocols in expected responder patients. A systematic review, including randomized controlled trials, found that the incidence of OHSS was significantly lower in antagonist cycles. Still, there was no difference between ongoing pregnancy and live birth rates (22). Because LH and HCG bind and activate LH/HCG receptors, oocyte instead of endogenous LH in COS Bolus HCG ensures maturation.

A recently published Cochrane meta-analysis comparing recombinant and urinary HCG found no difference between the agents regarding live birth and ongoing pregnancy rates (23). However, HCG's half-life (days) is much longer than endogenous LH's (hours). Therefore, bolus injection of HCG may lead to the development of OHSS with the formation of multiple corpus luteum due to the prolonged luteotropic effect (23).

In a study comparing r-LH with a shorter half-life with urinary HCG, it was shown that a single dose of r-LH (15.000 – 30.000 IU) was as effective as HCG in achieving final oocyte maturation, with a significant reduction in the incidence of OHSS compared to HCG (24). GnRH agonists are ovulation-triggering agents that are an alternative to HCG and are increasingly popular. The GnRH agonist replaces the antagonist at the receptor level and stimulates the receptor, increasing the release of gonadotropins with a flare-up effect. For this reason, GnRH agonists are often used in antagonist protocols to induce ovulation. However, the gonadotropin released by the GnRH agonist is at lower levels than in the natural cycle.

CONCLUSION

In conclusion, data showing the superiority of one gonadotropin option over another in IVF/ICSI treatment cycles are insufficient. The choice of gonadotropin in controlled ovarian stimulation depends on the product’s availability and should be based on ease of use and cost.

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Conflict of interest: The authors declare that they have no competing interests.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

Abbreviations

COS : Controlled ovarian stimulation

ET : Embryo transfer

E2 : Estradiol

FSH : Follicul stimulating hormone

GnRH : Gonadotropin-releasing hormone

HCG : Human corionic gonadotropin

HMG : Human menopausal gonadotropin

ICSI : Intracytoplasmic sperm injection

IUI : Intrauterine insemination

IVF : In-vitro fertilization

LH : Luteinizing hormone

LP : Luteal phase

OC : Oral contraceptives

OHSS : Ovarian hyperstimulation syndrome

OI : Ovulation induction

OPU : Ovum pick-up

PCOS : Polycystic ovary syndrome

PL : Premature luteinization

P4 : Serum progesterone

TESE : Testicular sperm extraction

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Comparison of Ykl-40 In Patients With &Without Gestational Diabetes Mellitus In The First Trimester &At Weeks 24 – 28

İlk Trimester ve 24-28. Haftada Gestasyonel Diyabeti Olan ve Olmayan Hastalarda Ykl-40 Düzeyinin Karşılatırılması

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Abstract

Objective: To elucidate whether the YKL-40 level in the first trimester is effective in predicting the development of diabetes in pregnant groups with and without gestational diabetes mellitus.
Methods: All first-trimester pregnant cases between the ages of 18 – 35 years who applied to the obstetrics and gynecology outpatient clinic of Antalya Training and Research Hospital with a single pregnancy, who did not have additional diseases and fetal anomalies, were included in the study (n=250). An oral glucose tolerance test of 75 gr (OGTT) was performed weekly to diagnose GDM in all pregnant women 24 – 28. During the administration of OGTT, fasting venous blood was taken to check the level of YKL-40.
Results: A total of 250 patients have been enrolled within the scope of this study. According to the results of OGTT, 18 individuals were diagnosed with GDM. Notably, while there was a difference in YKL-40 measurements in all patients, buts no difference in sub-group analysis. The differences between the first YKL-40, second YKL-40, and YKL-40 difference values of patients with and without GDM were evaluated. There was no statistically significant difference between the first, second, and YKL-40 difference values of patients with and without GDM ($p>0.05$).
Conclusion: Regarding the results of this research, YKL-40 might be valuable in detecting low-grade inflammation in pregnant women. However, there is a need for larger-scale prospective randomized studies from the early period to the end of pregnancy to better and more accurately evaluate the relationship between insulin resistance and inflammation.

Keywords: Gestational diabetes mellitus , HOMA-IR , YKL-40.

Özet

Amaç: Gestasyonel diabetes mellitusu(GDM) olan ve olmayan gebe gruplarında ilk trimesterdeki YKL-40 düzeyinin diyabet gelişimini öngörmede etkili olup olmadığını aydınlatmayı amaçladık.
Yöntem: Antalya Eğitim ve Araştırma Hastanesi kadın hastalıkları ve doğum polikliniğine tekil gebeliği bulunan, ek hastalığı ve fetal anomalisi olmayan 18 – 35 yaş arası tüm birinci trimester gebeleri çalışmaya alındı (n=250). GDM tanısı koymak için 24 – 28 haftalık gebelere 75 gr oral glukoz tolerans testi (OGTT) yapıldı. OGTT uygulaması sırasında, YKL-40 seviyesini kontrol etmek için açlık venöz kanı alındı.
Bulgular: Bu çalışma kapsamında toplam 250 hasta çalışmaya alındı. OGTT sonuçlarına göre 18 kişiye gestasyonel diabetes mellitus tanısı konuldu. Trigliserid değerleri farklıydı ($p<0.05$); her iki grup da ikinci trimesterde artmış seviyeler gösterdi. Özellikle, tüm hastalarda YKL-40 ölçümlerinde bir fark varken, alt grup analizinde fark bulunamadı. GDM'u olan ve olmayan hastaların birinci YKL-40, ikinci YKL-40 ve YKL-40 değerleri arasındaki istatistiksel olarak anlamlı fark saptanmadı ($p>0.05$). İkinci trimesterde trigliserit ve YKL-40 ölçümlerinde birinci trimestere göre artış gözlendi ($p<0.05$).
Sonuç: Bu araştırmanın sonuçları, YKL-40'ın düşük dereceli inflamasyonun saptanmasında değerli bir biyobelirteç olacağıdır. Bununla birlikte, insülin direnci ile inflamasyon arasındaki ilişkiyi daha iyi ve daha doğru bir şekilde değerlendirmek için erken dönemden gebeliğin sonuna kadar daha büyük ölçekli prospektif randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel Diabetes Mellitus, HOMA-IR, YKL-40.

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INTRODUCTION

Gestational diabetes mellitus (DM) is diabetes that begins and is first noticed during pregnancy. It is glucose intolerance independent of whether it continues after pregnancy and whether insulin is used in the treatment. Glucose intolerance is milder than Type I and Type II DM (1). Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 2 – 3% of all pregnant women. An average of 90% of pregnancies complicated with diabetes are gestational diabetes. Type 2 diabetes accounts for 8% of pregestational diabetes and type 1 diabetes for 2% (2).

Gestational DM is important not only for pregnancy outcomes but also for the mother and child's future. Gestational DM is an important part of the increasing prevalence of diabetes, regardless of genetics and other known risk factors for diabetes (3). Although glucose intolerance will return to normal after delivery in most cases, at least half of these women will develop diabetes (especially type 2 DM) in the future (14). Diabetes can be permanent in 3 – 20% of patients with gestational DM. Considering the studies conducted in the last 30 years, quite different results (34–87.5%) are reported among the rates of diabetes development after GDM (5).

The infant of a mother with gestational DM is at risk of developing obesity at an early age, impaired glucose intolerance, and diabetes. The risk of developing diabetes/prediabetes in children with gestational DM is almost eight times higher (6). The dominant view is that intrauterine hyperglycemia is an increased risk factor for diabetes in children and a several-fold increased risk factor for early-onset diabetes/prediabetes is the dominant literature (7). Because of all these, the diagnosis of GDM should be made, and the mother and child should be followed up after pregnancy (8).

YKL-40 is a 40 kDa glycoprotein secreted by many cells, including neutrophils, macrophages, and vascular smooth muscle cells. It has been found that the level of YKL-40 in the circulation is increased in many diseases characterized by acute and chronic inflammation (8 – 10). Twelve studies according to a review, serum YKL-40 level was high in patients with Type 2 DM. In addition, YKL-40 was defined as a marker in evaluating metabolic and inflammatory parameters in type 2 DM (11).

Within the scope of this research, we aimed to elucidate whether the YKL-40 level in the first trimester is effective in predicting the development of diabetes in pregnant groups with and without gestational diabetes mellitus.

METHOD

All first trimester (6-12 weeks) pregnant cases between the ages of 18 – 35 years who applied to the obstetrics and gynecology outpatient clinic of Antalya Training and Research Hospital with a single pregnancy, who did not have additional diseases and fetal anomalies, were included in the study (n=250). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 2016-016 and informed consent has been obtained from all participants.

All patients were questioned regarding gestational diabetes (GDM) risks such as age, previous pregnancy, smoking, alcohol, hypertension, chronic disease, and family history of diabetes. Weight, height, and blood pressure measurements were conducted in the examination. During

the initial admission in the first trimester (6 – 12th gestational week), fasting venous blood samples were taken from all patients. An oral glucose tolerance test of 75 gr (OGTT) was performed weekly to diagnose GDM in all pregnant women 24 – 28. GDM was diagnosed when one or more abnormal plasma glucose values, fasting ≥92 mg/dL, 1 hour ≥180 mg/dL, 2 hours 153 mg/dL, using the criteria of The International Association of Diabetes and Pregnancy Study Groups. During the administration of OGTT, fasting venous blood was taken to check the level of YKL-40. Blood clotting was stored at room temperature for at least 30 minutes, followed by centrifugation to separate the serum (2500 rpm, 15 min, 4°C). Serum samples were divided and stored at -80°C until the levels of yCL-40 were analyzed.

YKL-40 serum levels were compared in 18 randomly selected pregnant among 18 patients who developed GDM and other normal pregnant women (Human YKL-40 ELISA Kit, MyBioSource USA). Glucose levels are available from a commercially available kit (Beckman AU5800; Beckman Coulter Diagnostics, USA). Insulin levels were processed with a chemiluminescent test (AccessDxI800; Beckman Coulter, Inc., Fullerton, CA, USA). Patients were followed up until birth. Infant birth weights, delivery mode, and birth weeks were recorded.

Homeostatic model evaluation of insulin resistance (HOMA-IR) was calculated as follows:

- Fasting glucose (mmol/L) × fasting insulin (IU/mL)/22.5

Statistical Analysis

The analyses were performed with SPSS 22.0 package program. Descriptive statistics are presented with frequency, percentage, mean, standard deviation (SD) and median (median), minimum (min), and maximum (max) values. Shapiro Wilks test was used for the normality test. In analyzing the difference between the measurement values of the groups with and without GDM, the Mann-Whitney U test was used when the data did not match the normal distribution, and the student's t-test was used when the data did not match. In analyzing the differences between the lab values in the trimester, the Wilcoxon Peer Test was used when the data did not match the normal distribution, and the paired T-Test was used when the data did not match. P values less than 0.05 were considered statistically significant.

RESULTS

A total of 250 patients have been enrolled within the scope of this study. According to the results of OGTT, 18 individuals were diagnosed with gestational diabetes mellitus.

The differences between the first and last insulin, glucose, HOMA, triglyceride, and YKL-40 values were evaluated. According to the inter-peer difference test, an increase was observed in triglyceride and YKL-40 measurements in the second trimester compared to the first trimester ($p<0.05$; Wilcoxon Signed-Rank Test). (Table 1).

The laboratory parameters of patients with and without gestational diabetes in the first and second trimesters have been investigated, and only triglyceride values were different ($p<0.05$; Wilcoxon Signed Rank Test). (Table 2). Both groups elaborated on increased levels in the second trimester. Notably, while there was a difference in YKL-40 measurements in all patients, there was no difference in sub-group analysis.

Table 1. Descriptive Statistics Of The Study Population

	Category	n Mean ± Sd	Percentage Median (Range)
Family History	Yes	11	30,6%
	No	25	69,4%
Smoking	No	32	88,9%
	Yes	4	11,1%
Treatment	Diet	15	83,3%
	Insulin	3	16,7%
Delivery Method	Cesarean	18	50,0%
	Normal	18	50,0%
Age		27,00 ± 4,38	26,00 (19-39)
Gestational week		9,78 ± 2,21	10,20 (4,6-13,2)
BMI		24,74 ± 4,41	23,62 (17,6-37,9)
Gravida		2,28 ± 1	2 (1-4)
Birth Age		39,13 ± 0,95	39,20 (36-40,5)
Weigth		3369,28 ± 364,46	3390 (2540-4150)

Table 2. Analysis of Differences Between Patients' First And Last Laboratory Parameters

	n	Mean	SD	Median	Min	Max	p-value
Initial insulin	35	8,71	9,53	5,66	2,49	55,39	0,134
Second insulin	35	10,09	7,89	7,64	2,29	31,76	
Inıtial glucose	36	82,00	7,53	81,50	63,00	99,00	0,099
Second glucose	36	77,17	13,80	78,00	40,00	109,00	
Initial HOMA	36	1,77	2,27	1,12	,00	13,54	0,167
Second HOMA	36	1,99	1,73	1,42	,39	6,90	
Initial triglycerides	36	114,31	47,55	104,50	60,00	245,00	**<0,001***
Second triglycerides	36	182,39	63,85	178,50	68,00	324,00	
Inıtial YKL-40	36	1344,69	649,24	1142,60	286,40	2904,60	**0,030***
Second YKL-40	36	1637,84	718,95	1545,15	435,90	3550,90	

* p<0,05; Wilcoxon Signed-Rank Test analyzed all comparisons

The differences between the first YKL-40, second YKL-40, and YKL-40 difference values of patients with and without GDM were evaluated. There was no statistically significant difference between the first, second, and YKL-40 difference values of patients with and without GDM (p>0.05; Mann-Whitney U Test). (Table 3).

Table 3. Analysis Of Differences Between Measurements In The First And Second Trimesters Of Patients With And Without Gestational Diabetes

	GDM (+)							GDM (-)						
	n	Mean	SD	Med	Min	Max	p-value	n	Mean	SD	Med	Min	Max	p-value
Initial insulin	17	7,33	3,52	6,10	3,65	18,39	0,076#	18	10,01	12,90	5,10	2,49	55,39	0,711#
Second insulin	17	10,47	6,07	8,28	3,19	27,53		18	9,74	9,46	5,29	2,29	31,76	
Initial glucose	18	82,22	8,05	83,5	63,0	97,0	0,419#	18	81,78	7,20	81,00	71,00	99,00	0,121+
Second glucose	18	78,78	12,45	79,5	40,0	99,0		18	75,56	15,23	76,50	40,00	109,00	
Initial HOMA	18	1,41	,85	1,22	,00	4,09	0,071#	18	2,13	3,10	1,05	,49	13,54	0,845#
Second HOMA	18	2,03	1,30	1,54	,43	5,37		18	1,95	2,11	,96	,39	6,90	
Initial triglycerides	18	107,83	46,82	87,0	68,0	228,0	**0,001*#**	18	120,78	48,74	110,0	60,0	245,0	**0,004*#**
Second triglycerides	18	194,33	69,65	187,5	77,0	300,0		18	170,44	56,91	163,5	68,0	324,0	
Initial YKL-40	18	1392,78	759,46	1082,55	286,4	2686,1	0,099+	18	1296,59	534,92	1154,75	785,6	2904,6	0,199#
Second YKL-40	18	1709,23	701,29	1550,85	716,3	3550,9		18	1566,44	749,4	1545,15	435,9	3181,7	

* p<0,05; # Wilcoxon Signed Rank Test; + Paired Samples t Test

From the descriptive statistics of patients with and without GDM, family history, smoking, mode of delivery, age, gestational age, BMI, gravida, birth week, and weight status were compared (Table 4). According to the different tests, the normal birth rate was higher in those without GDM (p=0.008). In addition, the age of GDM patients was higher (p<0.001), gestational age was lower (p=0.006), BMI value was higher (p=0.033), and delivery week was lower (p=0.021).

Table 4. Analysis Of The Differences Between The First YKL-40, Second YKL-40 And YKL-40 Difference Values of Patients With And Without GDM

	GDM	Mean	SD	Median	Min	Max	p-value
Inıtial YKL-40	Yes	1392,78	759,46	1082,55	286,40	2686,10	0,874
	No	1296,59	534,92	1154,75	785,60	2904,60	
Second YKL-40	Yes	1709,23	701,29	1550,85	716,30	3550,90	0,613
	No	1566,44	749,40	1545,15	435,90	3181,70	
Difference in YKL-40	Yes	316,44	769,58	480,00	-1361,40	1470,00	0,527
	No	269,85	876,94	112,65	-1447,90	1960,60	

Analyzed with Mann-Whitney U Test

DISCUSSION

In the first trimester, due to the continuous transfer of glucose from mother to fetus, maternal plasma glucose is approximately 15 mg/dL lower than that of a non-pregnant woman of the same weight. Therefore, hypoglycemia is frequently seen in the first trimester. A similar decrease is observed in amino acid levels. Postprandial glucose levels remain elevated for longer due to increased peripheral resistance to insulin (12).

The first trimester is the phase in which gluconeogenesis increases. It is the anabolic phase in which maternal protein, glycogen, and fat stores increase. Estrogen and progesterone increase

insulin production and secretion by causing pancreatic beta-cell hyperplasia (13). Hyperinsulinism in early pregnancy is an event that increases lipogenesis and inhibits lipolysis. Glucagon level is suppressed in normal pregnant women. The catabolic phase develops in the second half of pregnancy (14). HPL (human placental lactogen), a polypeptide hormone secreted from syncytiotrophoblasts, increases proportionately to placental mass. Human placental lactogen is a potent insulin antagonist. The HPL increase, which starts at the tenth week of pregnancy, reaches 300 times at the twentieth week. Human placental lactogen stimulates lipolysis, increasing free fatty acids and peripheral insulin resistance (15).

A 44% decrease in insulin sensitivity was found in normal pregnancy in the third trimester. Increased insulin production easily compensates for this increase in insulin resistance in non-diabetic pregnant women (16). In diabetic patients with limited or no insulin reserve, increased insulin resistance leads to hyperglycemia as pregnancy progresses. Gestational diabetes occurs in women who can secrete sufficient insulin under normal conditions but cannot tolerate the increased insulin resistance of pregnancy. In addition to increased HPL levels, the level of triglycerides, free fatty acids, HDL (high-density lipoprotein), VLDL (Very Low-Density Lipoprotein), lipoproteins, and free cortisol in the blood contribute to hyperglycemia (17).

The infant of a mother with gestational DM is at risk of developing obesity at an early age, impaired glucose intolerance, and diabetes mellitus. The risk of developing diabetes/prediabetes in children with gestational DM is almost eight times higher (18). The fact that intrauterine hyperglycemia is an increased risk factor for diabetes in children and a several-fold increased risk factor for early-onset diabetes/prediabetes is the dominant view in the literature. Because of all these, the diagnosis of GDM should be accurately investigated, and the mother and child should be followed up after pregnancy (16 – 18).

A review by Deng et al. stated that serum YKL-40 levels increased in conditions characterized by inflammation, such as asthma, inflammatory bowel diseases, rheumatoid arthritis, psoriasis, atherosclerosis, colorectal cancer, small cell lung cancer, and stomach cancer (19). Gybel-Brask et al. have elaborated on the effectiveness of serum YKL-40 levels in detecting inflammation. Their study confirmed that not only serum YKL-40 levels but also inflammation-related neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLO) increases were shown in pregnant women with GDM (20). Regarding the results of our research, it was found that YKL-40 measurements were elevated in the second trimester compared to the first trimester.

Aktulay et al. indicated that YKL-40 was associated with insulin resistance that develops due to macrophage infiltration into adipose tissue (21). This is especially important in pointing out the relationship between inflammation and insulin resistance in obese people. Pregnancy is a condition characterized by insulin resistance, and the pancreas increases insulin secretion to overcome this resistance, and a hyperinsulinemic environment occurs. Insulin resistance in pregnancy is observed due to the anti-insulin effect of many placental hormones, such as human placental lactogen (HPL), human placental growth hormone, estrogen, progesterone, cortisol, and prolactin. It is expected to correlate with BMI and insulin resistance parameters (22).

Rinnov et al. reported that serum YKL-40 level was higher in the postpartum period compared to the third trimester of pregnancy. They found that serum YKL-40 level was positively correlated with IL-6, an inflammatory cytokine, confirming the close relationship between inflammation and YKL-40 (23). In a study by Li et al., serum YKL-40 level was found to be higher in pregnant women with GDM compared to healthy pregnant women, and

they found this level to be positively correlated with HbA1c value, fasting insulin level, and HOMA-IR value. In our study, while there was an increase in YKL-40 measurements in all patients, no difference in sub-group analysis (24).

A recent study by Tuten et al. emphasized that serum YKL-40 levels increased in pregnant women with GDM, and was positively correlated with insulin resistance parameters. They have also elaborated that although the fasting glucose level was similar in pregnant women with GDM compared to healthy pregnant women, the HbA1c level, which showed long-term glycemic control, was significantly higher. In addition, maternal serum YKL-40 level was positively correlated with HbA1c, fasting insulin, BMI, and HOMA-IR in decreasing order (25).

Regarding the results of this research, YKL-40 might be valuable in detecting low-grade inflammation in pregnant women. However, there is a need for larger-scale prospective randomized studies from the early period to the end of pregnancy to better and more accurately evaluate the relationship between insulin resistance and inflammation.

Funding: There is no specific funding related to this research.

Competing interests: The authors declare that they have no competing interests.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

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Evaluation Of The Frequency Of Malignancies In Patients Who Performed Gastroscopy And Colonoscopy Because Of Iron Deficiency Anemia

Demir Eksikliği Anemisi Nedeniyle Gastroskopi Ve Kolonoskopi Yapılan Hastalarda Malignite Sıklığının Değerlendirilmesi

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Abstract

Aim: In this study, we aim to present the results of patients in our clinic who underwent colonoscopy and gastroscopy because of iron deficiency.
Method: Patients who underwent gastroscopy and colonoscopy for the etiology screening of iron deficiency anemia in Ankara Ataturk Sanatorium Training and Research Hospital Gastroenterology Department between July 2021 and December 2022 were included in the study. Age, gender, anamnesis and endoscopic results of the patients were acquired retrospectively via investigation of patients files. SPSS 21.0 for statistical analysis Windows program used.Descriptive statistical methods(mean,standard) were used.
Results: The mean age of men was 63.6±7.4 years, and the mean age of women was 58.4±8.6 years. During this period, colonoscopy was requested in 576 (20%) of 2880 patients due to the etiology of iron deficiency anemia. Of the patients, 280 (48.6%) were male and 296 (51.4%) were female. Gastroscopy was performed in 496 of the cases. Although colonoscopy was normal, there were 40 (6.9%) patients who did not undergo gastroscopy. 205 (35.6%) patients had no endoscopic finding to explain anemia and 296 (51.4%) had no colonoscopic polyps or carcinomas and no colonoscopic findings to explain anemia. Colonoscopy was normal in 98 (17%) of the patients and there was no significant feature in esophagogastroscopy.
Conclusion: In the patients included in the study, polyps were detected in 52.4% of the patients and adenocarcinoma in 6.5% of the patients during colonoscopy.When investigating the cause of IDA, it should be kept in mind that there might be several underlying causes, especially if a pathology originating from the gastrointestinal tract is considered.

Keywords: Iron Deficiency Anemia, Gastroscopy, Colonoscopy.

Özet

Amaç: Bu çalışmada kliniğimizde demir eksikliği nedeniyle kolonoskopi ve gastroskopi yapılan hastaların sonuçlarını sunmayı amaçladık.
Yöntem: Temmuz 2021-Aralık 2022 tarihleri arasında Ankara Atatürk Sanatoryum Eğitim ve Araştırma Hastanesi Gastroenteroloji bölümünde demir eksikliği anemisi etiyoloji taraması için gastroskopi ve kolonoskopi yapılan hastalar çalışmaya dahil edildi. . Hastaların yaş, cinsiyet, anamnez ve endoskopik sonuçları retrospektif olarak hasta dosyaları incelenerek elde edildi. İstatistiksel analiz için SPSS 21.0 Windows programı kullanılmıştır. Tanımlayıcı istatistiksel yöntemler (ortalama, standart) kullanılmıştır.
Bulgular: Erkeklerin yaş ortalaması 63,6±7,4, kadınların yaş ortalaması 58,4±8,6 idi. Bu dönemde 2880 hastanın 576'sına (%20) demir eksikliği anemisi etiyolojisi nedeniyle kolonoskopi istendi. Hastaların 280'i (%48,6) erkek, 296'sı (%51,4) kadındı. Olguların 496'sına gastroskopi yapıldı. Kolonoskopi normal olmasına rağmen gastroskopi yapılmayan 40 (%6,9) hasta vardı. 205 (%35,6) hastada anemiyi açıklayacak endoskopik bulgu, 296 (%51,4) hastada kolonoskopik polip veya karsinom ve anemiyi açıklayacak kolonoskopik bulgu yoktu. Hastaların 98'inde (%17) kolonoskopi normaldi ve özofagogastroskopide anlamlı bir özellik yoktu.

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Sonuç: Çalışmaya dahil edilen hastalarda kolonoskopi sırasında hastaların %52,4'ünde polip, %6,5'inde adenokarsinom saptanmıştır. DEA nedeni araştırılırken altta yatan birkaç neden olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Demir Eksikliği Anemisi, Gastroskopi, Kolonoskopi.

INTRODUCTION

World Health Organization (WHO) defines anemia as hemoglobin poverty while the hemoglobin level is below 12 g/dl in adult women and below 14 g/dl in adult men. Iron deficiency anemia is more rare in men than women and is the most frequently seen kind of anemia(1). Iron deficiency anemia is not an illness. Experts should examine and elicit the etiology for every patient (2). In different ages, the rate of etiological reasons of iron deficiency anemia differs. In premenopausal women, the most common reason of iron deficiency anemia is menstrual bleeding. Nevertheless in adult men and postmenopausal women, the most common reason of iron deficiency anemia is chronic blood losses from the gastrointestinal tract (3). The cause of IDA was found in 48-71% of patients who underwent upper and lower endoscopic procedures; while in unexplained cases, it was reported that overlooked lesions were determined in 35% of the cases that underwent repeat endoscopic procedure. In fact, the success in the diagnosis of IDA has increased to 61-74% with the examination of the small intestine (capsule endoscopy or double balloon enteroscopy) in anemia that continues despite endoscopic examinations recently (4). In this study, we aim to present the results of patients in our clinic who underwent colonoscopy and gastroscopy because of iron deficiency.

METHOD

Patients who underwent gastroscopy and colonoscopy for the etiology screening of iron deficiency anemia in Ankara Ataturk Sanatorium Training and Research Hospital Gastroenterology Department between July 2021 and December 2022 were included in the study. The study was carried out with the permission Ankara Ataturk Sanatorium Training and Research Hospital Ethics Committee (Date: 13/02/2023, Decision No:209039370). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki Informed consent was obtained during the procedure and the data were evaluated retrospectively. Age, gender, anamnesis and endoscopic results of the patients were acquired retrospectively via investigation of patients files. Patients who were followed up and treated for hematological and oncological malignancies, patients admitted with gastrointestinal bleeding, patients under 18 years of age, patients with chronic renal and hepatic failure, previously identified malignancy, previous gastric and intestinal resection, known inflammatory bowel disease, malabsorption were not included in the study.

Statistical Analysis

SPSS 21.0 for statistical analysis Windows program used. Descriptive statistical methods(mean,standard)were used.

RESULTS

During this period, colonoscopy was requested in 576 (20%) of 2880 patients due to the etiology of iron deficiency anemia. Of the patients, 280 (48.6%) were male and 296 (51.4%) were female. The mean age of men was 63.6±7.4 years, and the mean age of women was 58.4±8.6 years. Gastroscopy was performed in 496 of the cases. Although colonoscopy was normal, there were 40 (6.9%) patients who did not undergo gastroscopy. 205 (35.6%) patients

had no endoscopic finding to explain anemia and 296 (51.4%) had no colonoscopic polyps or carcinomas and no colonoscopic findings to explain anemia. Colonoscopy was normal in 98 (17%) of the patients and there was no significant feature in esophagogastroscopy. However, a total of 357 (61.9%) patients had either gastroscopic or colonoscopic findings that could explain the anemia. Polyps were detected in 300 (52.4%) patients and carcinoma in 38 (6.5%) patients during colonoscopy. Considering the number of polyps in patients with polyps, one polyp was removed in 168 patients, two polyps in 58 patients, three polyps in 46 patients, five polyps in 20 patients, and six polyps in 8 patients. Considering the diameters of the polyps, 195 (65%) diminitive polyps with <0.5 cm diameter, 36 (12%) with 1 cm diameter, 32 (10.6%) with 1.5 cm diameter, 20 (6%) with 2 cm diameter There were .6) polyps with a diameter of 3 cm and 17 (5.6%) polyps. Considering the degree of dysplasia of the polyps, 122 (40.6%) had a mild degree of dysplasia. When we examine the total polyp localizations; 114 (38%) in the sigmoid colon, 54 (18%) in the rectum, 36 (12%) in the descending colon, 33 (11%) in the transverse colon, 33 (11%) in the ascending colon and 30 (10%) were found in the cecum. When the histological types of polyps are examined, 210 (70%) hyperplastic polyps, 73 (24.3%) adenomatous polyps; 42 (57.5%) were tubular adenomas, 21 (28.7%) were tubulovillous adenomas, and 10 (13.8%) were villous adenomas. 4 (1.3%) were reported to have mild chronic inflammation and regenerative changes, and 3 (1%) were reported as inflammatory polyps. Polyps with other histological features were 10 (3.4%). 40 (13.3%) of the patients with polyps had a family history of colonic ca or polyp. Of the patients with polyps, 10 (3.3%) had a history of alcohol use more than 50 g/day, 65 (21.6%) had a history of smoking over 25 packs/year, and 42 (14%) had a history of smoking under 25 packs/year . There was a long history of active smoking (Table 1).

Table 1. Characteristics Of Patients With Polyps Detected By Colonoscopy

Total Number of Patients	Total Number of Polyps	
Localization	Sigmoid colon	38%
	Rectum	12%
	Transvers colon	11%
	Descending colon	12%
	Ascending colon	11%
	Cecum	**10**%
Polyp Diameter	0,5 cm	**65**%
	1 cm	12%
	1,5 cm	0.6%
	2 cm	6.6%
	3 cm	5.6%
Histopathological Types	Hyperplastic polyp	70%
	Tubular adenoma	14%
	Tubulovillous adenoma	7%
	Villous adenoma	3.3%
	Mild chronic inflammation	1.3%
	Inflammatory polyp	1%
	Dimer disease types	63.4%
Cigarettes and Alcohol	65 patient >25 pack year cigarette squits moking	
	42 patients <25 pack year cigaretteusing	

	10 patients >50 gr/day heavy alcohol drinker

When we look at the localizations of those with colon cancer, 18 (47.3%) are in the sigmoid colon, 6 (15.7%) are in the rectum, 6 (15.7%) are in the descending colon, and 4 (10.5%) are ascending colon, 3 (7.8%) in the cecum, 1 (3.8%) in the transverse colon. When the histological type of colon ca was examined, adenocarcinoma was detected in all of them. Among these patients, 12 (31.5%) had a family history of colonic ca, 17 (50%) had a smoking history for more than 20 years, and 4 (10.5%) had a history of alcohol use less than 30 g/day. The others had no smoking or alcohol consumption history. When the BMI of the patients was examined, it was seen that 4 of them were >30, 6 of them were <25 and the others were between 25-30 (Table 2).

Table 2. Characteristics of patients with malignancies detected by colonoscopy

Histopathological Type	Adenokarsinoma	
Localization	Sigmoid colon	47.3%
	Rectum	15.7%
	Descending colon	15.7%
	Ascending colon	10.5%
	Cecum	7.8%
	Transvers colon	3.8%
Cigarettes and Alcohol	17 patients> 20 pack year cigarettes	
	4 günde <30 gr/day alcohol	
BMI	>30 four patients	
	<25 six patients	
	25 - 30/tywenty five patients	

Cardiac adenocarcinoma was detected in 1 and Barret's esophagus in 1 of the patients who underwent gastroscopy. Among the patients, 60 had pathologically diagnosed chronic active gastritis, 36 had ulcers, 55 had hyperplastic polyps, 6 had esophageal varices, 36 had esophagitis, and 16 had hiatal hernia. Duodenal biopsy was taken for celiac in 47 of the patients and celiac disease was detected in 24 patients. Biopsies were obtained from 496 patients for Helicobacter pylori and intestinal metaplasia. Among these, 236 had Helicobacter pylori and 113 had intestinal metaplasia. There was an endoscopic finding that could explain anemia in a total of 68.8 % of patients.

DISCUSSION

After the confirmation of iron deficiency anemia via laboratory studies endoscopic examination of the gastrointestinal tract should be initiated. Before the endoscopic examination, exclusion of such possible anemia reasons is necessary; dietary iron deficiency, increased iron requirement and extra-gastrointestinal blood loss.

Two important causes of iron deficiency are chronic blood loss and iron absorption disorders. Both conditions are closely related to the gastrointestinal system. In gastrointestinal applications due to iron deficiency; it was determined that the reason of iron deficiency was gastrointestinal in 43-86% of different patient groups (5-11).

For patients with iron deficiency, the most common diagnoses is gastrointestinal system cancers. In gastrointestinal system endoscopic examinations performed in patients with iron deficiency anemia, the rate of malignancy has been reported to vary between 6% and 13% (5-11). In a study which is conducted in Turkey due to iron deficiency anemia, it was reported that malignancy was found at a rate of 3.81% in gastroscopy and 8.6% in colonoscopy (5). In another study which is conducted in Turkey, adenocarcinoma was diagnosed in 0.9% of patients who underwent upper gastrointestinal endoscopy and in 4.7% of patients who underwent lower gastrointestinal system endoscopy in patients who were examined because of iron deficiency anemia. Again in this study, the frequency of polyp detection in colonoscopy was reported to be 45% (12). Although the diagnostic benefit of esophagogastroscopy is higher than colonoscopy , colonoscopic examination is necessary even in the presence of a benign upper gastrointestinal lesion to explain anemia, especially in the elderly (13-15). Detection of significant colonic malignancy in patients with benign upper gastrointestinal lesion necessitates whole colon examination(16-20).

In the patients included in the study, polyps were detected in 52.4% of the patients and adenocarcinoma in 6.5% of the patients during colonoscopy, and their detailed characteristics are mentioned in Tables 1 and 2. Neoplastic lesion (polyp or cancer) was detected in the colon with a total rate of 61.9%. The most common lesion in gastroscopy was gastritis (72.3%). In addition, gastroscopy revealed adenocarcinoma in 0.02% and Barret's esophagus, which was premalignant in 0.02%. Polyps were found in 11%, celiac disease in 4.8%, and esophageal varices and liver cirrhosis in 1.2%. These ratios show that both processes should be done together. In addition, although only 47 patients had a biopsy for celiac, 24 (51%) were positive for celiac, suggesting that routine duodenal biopsy should be performed in the investigation of the etiology of iron deficiency anemia.

CONCLUSION

In conclusion, when investigating the cause of IDA, it should be kept in mind that there might be several underlying causes, especially if a pathology originating from the gastrointestinal tract is considered. Among these reasons, malignancies, which are the most important diseases, have an important place. Considering that the frequency of colorectal cancer is higher than gastric cancer today; it is suggested that colonoscopy should be performed firstly, and if the colonoscopy result is negative, then gastroscopy should be performed.

Ethics Committee Approval: The study was carried out with the permission of XXX Training and Research Hospital Ethics Committee (Date: 13/02/2023, Decision No:209039370).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Clinical Features & Early Treatment Outcomes Of Children With Crush Syndrome After Kahramanmaraş Earthquake

Kahramanmaraş Deprem Sonrası Crush Sendromlu Çocukların Klinik Özellikleri Ve Erken Tedavi Sonuçları

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Abstract

Objective: Extensive muscle crush injury that results in crush syndrome is often fatal if not treated promptly and vigorously. Although cases of Crush syndrome experienced by adults were frequently published in the previous literature, data on Crush syndrome in children are limited. In this study, we aimed to elucidate the clinical and laboratory findings of children with Crush syndromewho applied to our institution after the earthquake.
Methods: Thirty-eight children with crush syndrome who applied to our institution after the earthquake disaster have been enrolled in this retrospective analysis. Demographic, clinical, and laboratory characteristics and early outcomes of children with crush wounds have been evaluated retrospectively. All children with crush wounds have been included in the analysis. Age, sex, height, and weight of the patient, admission and follow-up laboratory parameters, presence of comorbid diseases, and transcutaneous oximetry measurement results have been obtained from the hospital's electronic database.
Results: The stay under wreckage ranged from 4 to 160 hours, averaging 30 hours. The mean length of hospital stay was 13days, and the length of intensive care unit stay was seven days. There was a statistically significant difference between the initial and final measurements of WBC, PLT, CRP, glucose, BUN, creatinine, AST, ALT, LDH, uric acid, CK, and albumin values ($p<0.05$). Children with multiple extremity involvementhad significantly elevated initiallaboratory measurements, while those with single extremity involvement presented higher values in the final measurements ($p<0.05$).
Conclusion: The high creatine kinase levelsmight indicate the severity of muscle damage in Crush syndrome. Elevated creatine kinase could be used to indicatemortality in these patients. Early assessment of compartment pressure can eliminate the risk of amputation. Rapid diagnosis and aggressive fluid resuscitation in the emergency department can prevent acute kidney injury or failure.

Keywords: Crush Syndrome, Extremity İnvolvement, Fasciotomy, Debridement, Earthquake.

Özet

Amaç: Crush sendromuyla sonuçlanan yaygın kas ezilme yaralanması, hızlı ve kuvvetli bir şekilde tedavi edilmezse genellikle ölümcüldür. Önceki literatürde yetişkinlerin yaşadığı Crush sendromu vakaları sıklıkla yayınlanmış olsa da, çocuklarda Crush sendromuna ilişkin veriler sınırlıdır. Bu çalışmada deprem sonrası kurumumuza başvuran Crush sendromlu çocukların klinik ve laboratuvar bulgularının aydınlatılmasını amaçladık.
Yöntem: Bu retrospektif çalışmaya deprem felaketi sonrası kurumumuza başvuran ezilme sendromlu 38 çocuk dahil edildi. Ezilme yarası olan çocukların demografik, klinik ve laboratuvar özellikleri ile erken dönem sonuçları retrospektif olarak değerlendirildi. Ezilme yarası olan tüm çocuklar analize dahil edilmiştir. Hastanın yaşı, cinsiyeti, boyu, kilosu, başvuru ve takip laboratuvar parametreleri, eşlik eden hastalık varlığı ve transkutan oksimetre ölçüm sonuçları hastanenin elektronik veri tabanından elde edildi.

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Bulgular: Enkaz altında kalma süresi 4 ile 160 saat arasında değişerek ortalama 30 saat olmuştur. Ortalama hastanede kalış süresi 13 gün, yoğun bakımda kalış süresi ise yedi gündü. WBC, PLT, CRP, glukoz, BUN, kreatinin, AST, ALT, LDH, ürik asit, CK ve albümin değerlerinin başlangıç ve son ölçümleri arasında istatistiksel olarak anlamlı fark vardı ($p<0,05$). Birden fazla ekstremite tutulumu olan çocuklarda ilk laboratuvar ölçümlerinde anlamlı olarak yüksek bulunurken, tek ekstremite tutulumu olanlarda son ölçümlerde daha yüksek değerler saptandı ($p<0.05$).
Sonuç: Yüksek kreatin kinaz seviyeleri, Crush sendromunda kas hasarının şiddetini gösterebilir. Yüksek kreatin kinaz bu hastalarda mortaliteyi belirtmek için kullanılabilir. Bölme basıncının erken değerlendirilmesi amputasyon riskini ortadan kaldırabilir. Acil serviste hızlı tanı ve agresif sıvı resüsitasyonu, akut böbrek hasarını veya yetmezliğini önleyebilir.

Anahtar Kelimeler: Crush Sendromu, Ekstremite Tutulumu, Fasyotomi, Debridman, Deprem.

INTRODUCTION

Crush syndrome is a form of traumatic rhabdomyolysis characterized by systemic involvement that occurs after prolonged continuous pressure. Extensive muscle crush injury that results in crush syndrome is often fatal if not treated promptly and vigorously (1).

Damages appear after prolonged pressure is applied to a muscle group. Pressure causes muscle necrosis, and during revascularization, calcium, sodium, and water diffusion into damaged muscle cells, accompanied by loss of potassium, phosphate, lactic acid, myoglobin, and creatinine kinase. These changes can lead to hyperkalemia, acidosis, acute renal failure, and hypovolemic shock (2). These patients may also develop serious local or systemic infections complicated by disseminated intravascular coagulation (DIC). Myoglobin causes kidney damage through mechanisms that are not fully defined. If renal failure develops, hemodialysis is started (3).

Indications for fasciotomy are the absence of a distal pulse or open lesions. When a fasciotomy is performed, the entire necrotic muscle must be radically removed (4). Crush syndrome is usually encountered in war zones, mining disasters, earthquakes, and occupational and traffic accidents. The first cases of Crush syndrome were identified during the Sicilian earthquake in Messina in 1909. Also 1940, the relationship between crush syndrome and myoglobinuric acute renal failure was reported (5). Difficulties with communication and transportation during a disaster often preclude early rescue and therapeutic interventions. Early extraction and intravenous fluid administration prevent failure (6).

A violent earthquake happened at4:17 a.m. and 1:24 p.m. on February 6, 2023, in southeastern and northwest regions of Turkey for 60 and 45 seconds, respectively, and thousands of sleeping families have buried graves. The earthquake's epicenter was Kahramanmaras,recorded on the Richter scale as 7.7 and 7.6, respectively.

Although cases of Crush syndrome experienced by adults were frequently published in the previous literature, data on Crush syndrome in children are limited.

Within the scope of this research, we aimed to elucidatethe relationshipbetween creatinine kinase, fasciotomy, and amputation rate. Additionally, we have investigated whether creatinine kinase is affected by the duration of stay in wreckageafter the earthquake.

METHOD

Thirty-eight children with crush syndrome who applied to our institution after the earthquake disaster have been enrolled in this retrospective analysis. All procedures were followed in

accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution at 03/03/2023 with protocol number 332. As this was retrospective research, no informed consent was obtained from participants or their legal representatives.

Demographic, clinical, and laboratory characteristics and early outcomes of children with crush wounds have been evaluated retrospectively. All children with crush wounds have been included in the analysis. Age, sex, height, and weight of the patient, admission and follow-up laboratory parameters, presence of comorbid diseases, and transcutaneous oximetry measurement results have been obtained from the hospital's electronic database.

Statistical Analysis

The patient data collected within the scope of the study were published in the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp. Harmonik. NY) was analyzed with the package program. Frequency and percentage were given as the categorical data's mean, standard deviation, median, minimum, and maximum descriptive values. "Independent Sample T Test" or "Mann Whitney U Test" for the two groups in the intergroup comparisons, "Paired Sample T-Test" or "Wilcoxon test" for the evaluation ofthe difference between the first and last measurement values, "Chi-square or Fisher's Exact Test" for the evaluation of categorical variables Test" was used. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 38 children have been enrolled within the scope of this research. The gender distribution could be elaborated as follows: 52.6% (n=20) were female, and 47.4% (n=18) were male. The mean age of the patients was ten years rangingbetween 1 to 17 years. The stay under wreckage ranged from 4 to 160 hours, with an average time of 30 hours. The mean length of hospital stay was 13 days(minimum two days, maximum 35 days),and the length of intensive care unit stay was seven days(minimum 0days, maximum 28 days).Intubation and mechanical ventilation have been performed on one patient each, respectively.The injured extremity involvement could be elaborated as the bottom left (n=27), lower right(n=23), upper left (n=9), and upper right (n=7).Fasciotomy has been performed on different areas: bottom left (n=12), lower right (n=9), and upper left (n=5).Amputation has been performed on eight patients, and debridement on 17. An infection has been observed in 38 children, and sepsis in only one child. The distribution of baseline demographics and clinical features of the patients are elaborated in Table 1.

The distribution of the first and last laboratory measurements of the patients is given in Table 2. When the table is examined, it was determined that there was a statistically significant difference between the initial and final measurements of WBC, PLT, CRP, Glucose, BUN, creatinine, AST, ALT, LDH, uric acid, CK, and albumin values ($p<0.05$).The median CK level at admission was 18.1U/L(range 1.8 – 330U/L) and 208 U/L(range 1.5 – 919 U/L) at the final measurement,and this difference was statistically significant ($p<0.001$). On the contrary, CK–MB values at admission and final follow-up did not reach significance (97.2 U/L range 19.6 – 466U/L versus 77.5 U/L range 18.5 – 432 U/L respectively, $p<0.070$).

Table 1. Distribution of Demographic and Clinical Findings of Patients

Variables (N=38)	n (%)	Average ± SD	Median (Min-Max)
Age (years)		10±4.4	9 (1-17.4)
Height (cm)		132.6±24.4	135 (72-172)
Weight (kg)		37±15.5	32 (12-64)
Gender			
Female	20 (52.6)		
Male	18 (47.4)		
Wreckageperiod (hours)		30.3±37.4	13 (4-160)
Protein in Urine		135.7±135.4	68 (68-338.7)
Hyperbaric O_2 Treatment	38 (100)		
Hospitalization (days)		13.1±8.2	11 (2-35)
ICU stay (days)		7±6.3	6.7 (0.2-27.7)
Intubation	1 (2.6)		
Mechanical Ventilation	1 (2.6)		
Sepsis	1 (2.6)		
Injured extremity			
Upper right	7 (18.4)		
Upper left	9 (23.7)		
Lower right	23 (60.5)		
Bottom left	27 (71.1)		
Fasciotomy	17 (44.7)		
Anatomical region			
Upper left	5 (29.4)		
Lower right	9 (52.9)		
Bottom left	12 (70.6)		
Debridement	17 (44.7)		
Amputation	8 (21.1)		
Amputation direction			
Upper left	2 (25)		
lower right	6 (75)		
Bottom left	7 (87.5)		
Infection	38 (100)		
Blood Transfusion	2 (9.1)		
Wound KX	6 (66.7)		

The distribution of demographic characteristics according to the involvement of one or more extremities is given in Table 3. When the table was examined, there was no statistically significant difference between the two groups in all demographic and clinical findings.

Table 2. Distribution of Laboratory Measurements of Patients

Variables	First Measurement		Final Measurement		p-value
	Average ± SD	Median (Min-Max)	Average ± SD	Median (Min-Max)	
WBC	**14.1±6.5**	**11.8 (5.6-34.9)**	**11.4±4.9**	**10.7 (4.7-27.5)**	**0.028**
Hemoglobin	12.1±5.4	10.4 (7.3-36.7)	12.5±12	9.4 (6.9-79)	0.790
HCT	36±11.2	33.9 (22.7-82.2)	32.8±13.6	30.1 (5.4-82.2)	0.150
PLT	**309.3±127.9**	**313 (91-593)**	**431.8±189.8**	**436 (59-915)**	**<0.001**
CRP	**65.3±54.6**	**41.9 (2-160.9)**	**23±41.1**	**4.1 (2-203.8)**	**<0.001**
PT	65.3±23.8	73 (7-98)	67±22	72.5 (13-98)	0.645
APTT	33.4±18.6	28.6 (17.8-102.1)	32.4±16.3	29.5 (16.1-96.3)	0.778
INR	1.3±0.3	1.2 (1-2.5)	1.2±0.4	1.2 (1-3.6)	0.760
Fibrinogen	358.7±147.1	369 (24-671)	304.2±130.3	316 (22-546)	0.068
Glucose	**143.7±90.2**	**113.5 (74-446)**	**106.5±47.3**	**96.5 (65-324)**	**0.009**
BUN	**82.8±84**	**40 (4-343)**	**29.7±15.8**	**26 (10-90)**	**<0.001**
Creatinine	**1±1.3**	**0.5 (0.3-5)**	**0.6±0.5**	**0.4 (0.1-2.8)**	**0.015**
AST	**594.4±636.3**	**336 (31-3004)**	**93.6±177.2**	**33.3 (8-891.5)**	**<0.001**
ALT	**332.4±475**	**240 (29-2986)**	**68±94.8**	**33.5 (9-536)**	**0.002**
LDH	**1765.1±2502.1**	**1022 (22.1-10023)**	**475.8±378**	**393.5 (44-2201)**	**0.001**
Uric Acid	**6.3±5.3**	**4.1 (1.8-20)**	**3±1.3**	**2.8 (0.9-7.8)**	**<0.001**
CK	**45.2±65.3**	**18.1 (1.8-330)**	**258.8±249.6**	**208 (1.5-919)**	**<0.001**
CK-MB	137.1±127.2	97.2 (19.6-466)	119.7±118	77.5 (18.5-432)	0.070
Albumin	**24.9±7.1**	**25 (13-44)**	**31.4±9.5**	**34 (6-49.1)**	**<0.001**
Na	134.9±8.2	135 (121-162)	134.3±16.6	137 (37-144)	0.827
K	4.6±1.3	4.2 (3.1-9.2)	4.7±1.5	4.4 (3.2-9.5)	0.802
Ca	7.9±1	7.9 (5.3-10.1)	8.3±1.8	8.8 (1.8-10.5)	0.274
Fosfor	4.8±2.5	4.5 (1.4-12.1)	4.5±1.2	4.4 (1.4-6.1)	0.340

The distribution of laboratory measurements according to the involvement of one or more extremities is given in Table 4. When the table was examined, it was seen that there was a statistically significant difference between the two groups in the baseline WBC, uric acid, potassium values, and final WBC, albumin, and calcium measurements ($p<0.05$).Children with multiple extremity involvementhad significantly higher initiallaboratory measurement levels, while this was vice versain those with single extremity involvement, as they presented higher values in the final measurements.

Table 3. Distribution of Demographic and Clinical Findings of Patients with Single and MultipleExtremity Involvement

Variables	Single extremity (n=14)			Multiple extremity(n=24)			p-value
	n (%)	Average± HR	Median (Min-Max)	n (%)	Average± HR	Median (Min-Max)	
Age (years)		10.8±5.6	10.4 (2-17)		9.9±3.5	9 (1-17.4)	0.614
Height (cm)		133.9±30	133.5 (76-172)		131.8±21.1	135 (72-162)	0.794
Weight (kg)		38.3±17.9	34 (12-61)		36.3±14.3	32 (14-64)	0.702
Gender							0.151
Female	10 (71.4)			10 (41.7)			
Male	4 (28.6)			14 (58.3)			
Time spent in the wreckage (hours)		28.2±39.8	14 (4.5-160)		31.5±36.7	11.5 (4-128)	0.798
Hospitalization (days)		13.2±9.8	14 (2-35)		13±7.4	11 (2-35)	0.925
ICU hospitalization (days)		7.3±7.4	6.4 (0.2-27.7)		6.8±5.8	6.7 (0.8-27.7)	0.855
Intubation	0 (0)			1 (4.2)			1.000
Mechanical Ventilation	0 (0)			1 (4.2)			1.000
Fasciotomy	7 (50)			10 (41.7)			0.873
Debridement	7 (50)			10 (41.7)			0.873
Amputation	2 (14.3)			6 (25)			0.684
Blood transfusion	0 (0)			2 (13.3)			1.000
Wound K-X	2 (66.7)			4 (66.7)			1.000

Table 4. Distribution of Laboratory Measurements of Patients with Single and MultipleExtremity Involvement

Measurements	Single extremity (n=14)		Multiple-extremity (n=24)		p-value
	Average±HR	Median (Min-Max)	Average±HR	Median (Min-Max)	
First-WBC	**10.7±3.9**	**10.4 (5.6-21.8)**	**16.2±7**	**13.8 (8.6-34.9)**	**0.004**
Final-WBC	**8.8±2.6**	**9.2 (4.7-13.4)**	**12.9±5.4**	**11.4 (6.7-27.5)**	**0.011**
First-Hb	12.9±8.1	10.2 (7.8-36.7)	11.6±3.1	11 (7.3-20.4)	0.582
Final-Hb	12.6±6.9	9.7 (7.9-30.5)	12.5±14.3	9.3 (6.9-79)	0.985
First-HCT	34.2±7.5	34.1 (23.9-50.2)	37.1±13	33.4 (22.7-82.2)	0.453
Final Hct	29.9±8.1	30.1 (5.4-39.1)	34.5±15.9	29.2 (22.9-82.2)	0.318
First-Plt	295.9±113.7	315.5 (91-469)	317.1±137.2	306.5 (107-593)	0.628
Final Plt	474.9±121.4	478 (258-707)	406.7±218.7	361.5 (59-915)	0.291
First-CRP	49.6±53.5	20.1 (6.5-153.7)	73.7±54.4	70.8 (2-160.9)	0.204
Final-CRP	10.3±25.4	2 (2-93.9)	29.9±46.5	12.3 (2-203.8)	0.170
First-PT	69.7±25.2	80.5 (12-92)	63.1±23.4	62.5 (7-98)	0.446
Final-PT	72.8±22.4	78.5 (13-91)	64.1±21.6	70.5 (14.2-98)	0.273
First-APTT	28.2±5.8	27.1 (23-45)	36±22.1	29 (17.8-102.1)	0.114
Final APTT	27.6±4.5	26.5 (21.8-39.4)	34.8±19.4	30.1 (16.1-96.3)	0.216
First-INR	1.3±0.4	1.1 (1.1-2.5)	1.2±0.2	1.2 (1-1.9)	0.652
Final-INR	1.1±0.1	1.1 (1-1.4)	1.3±0.5	1.2 (1-3.6)	0.370
First-Fibrinogen	313.4±207.1	385 (24-563)	372.8±128.6	366.5 (219-671)	0.445
Final-Fibrinogen	250±165.6	274 (22-462)	321.1±118.4	328 (140-546)	0.298
First-Glucose	157.6±120.4	106 (75-446)	135.6±68.7	120 (74-408)	0.540
Final-Glucose	110±62	96.5 (84-324)	104.4±37.7	97.5 (65-245)	0.731
First-BUN	59.7±67.5	30 (4-218)	95.3±90.6	52.5 (10-343)	0.223
Final-BUN	26.5±8.9	26 (13-42)	31.4±18.4	29 (10-90)	0.369
First-Creatine	0.9±0.9	0.6 (0.3-3.1)	1.1±1.5	0.5 (0.3-5)	0.679
Final-Creatine	0.5±0.2	0.5 (0.1-0.9)	0.6±0.6	0.4 (0.3-2.8)	0.682
First-AST	378.2±395.6	255 (31-1527)	720.5±719.6	452.5 (33-3004)	0.111
Final-AST	45.2±34.2	32.5 (16-140)	121.8±218.1	45 (8-891.5)	0.104
First-ALT	207±152	219.5 (29-562)	405.6±578.5	298 (76-2986)	0.218
End-ALT	45.8±52.8	32 (9-185)	80.9±111.4	36.7 (9-536)	0.277
First-LDH	1086.8±918.9	881 (132-3025)	2160.7±3025.1	1071 (22.1-10023)	0.117
Final-LDH	323.2±140.3	295 (44-530)	564.8±443	466 (46.3-2201)	0.056
First-Uric-Acid	**4±3.1**	**3.2 (1.8-13.4)**	**7.6±5.9**	**5.6 (1.9-20)**	**0.018**
Final-Uric-Acid	3.1±0.9	2.9 (1.6-5.2)	2.9±1.6	2.8 (0.9-7.8)	0.736
First-CK	46.8±86.4	13.4 (1.8-330)	44.2±51.4	18.1 (3.2-167.2)	0.909
Final-CK	216.8±183.2	147 (1.5-629)	283.3±282.1	217 (1.5-919)	0.435
First-CK-Mb	69.6±55.1	50.4 (26.9-150.4)	164.1±139.8	147.2 (19.6-466)	0.222
Final- CK-Mb	76.1±52.6	70.1 (22.1-142.1)	137.1±134.2	98 (18.5-432)	0.404
First-Albumin	25.1±6	25.5 (13-34)	24.7±7.7	24 (13.8-44)	0.884
Final -Albumin	**35.8±8.1**	**36 (13-49.1)**	**28.8±9.4**	**28.6 (6-44)**	**0.026**
First-Na	137±5.7	136.5 (128-150)	133.8±9.3	134 (121-162)	0.246
Final -Na	137.9±2.7	138.5 (133-142)	132.3±20.6	137 (37-144)	0.321
First-K	**4.1±0.5**	**4.1 (3.4-5.2)**	**4.9±1.5**	**4.8 (3.1-9.2)**	**0.023**
Final -K	4.4±0.4	4.5 (3.9-5)	4.8±1.8	4.3 (3.2-9.5)	0.314
First-Ca	8.3±0.9	8.4 (6.7-9.9)	7.7±1	7.4 (5.3-10.1)	0.055
Final-Ca	**9.1±0.4**	**9.2 (8.1-10)**	**7.8±2.1**	**8.5 (1.8-10.5)**	**0.007**
First-Phosphorus	4.5±1.2	4.5 (2.6-6.5)	5±3	4.2 (1.4-12.1)	0.483
Final-Phosphorus	4.8±0.8	4.7 (3.1-6.1)	4.3±1.4	4.3 (1.4-6.1)	0.245

DISCUSSION

Trauma types seen during earthquakes differ according to the infrastructure characteristics of the countries. For example, when all hospital admissions were reviewed during the 2005 Battagram, Pakistan Earthquake, it was reported that superficial traumas such as laceration and contusion were the most common, followed by orthopedic extremity trauma, head trauma, thoracic trauma, and closed abdomen trauma (7). In the 2011 Van, Turkey Earthquake, 95% of the disaster victims were brought to hospitals with soft tissue trauma, followed by multiple extremity fractures and compartment syndrome (8). In the Southern Italy Earthquake, approximately half of the disaster victims were injured in more than one part of the body; here, too, the most frequently reported injury type was laceration, followed by contusions, fractures, and cuts (9). One of the most detailed documentation on earthquake traumas was made after the Hanshin-Awaji Earthquake in Japan. In the first 15 days after the disaster, earthquake-related traumas were found in 2718 out of 6107 patients in the examination admission to 95 hospitals. Extremity, spine, pelvis, and other fractures were recorded most frequently in this patient group. Soft tissue traumas, including contusions, lacerations, and cuts, occurred in 35.1%; crush syndrome developed in 372 patients, and peripheral nerve damage was detected in 131 patients (10). When extra-extremity traumas were examined in patients with crush syndrome in the Kobe Earthquake and the Marmara Earthquake in our country, thoracic and abdominal traumas with a high mortality rate were followed by head and pelvis traumas (11). In our study, the injured extremity involvement could be elaborated as the bottom left (n=27), lower right (n=23), upper left (n=9), and upper right (n=7).Fasciotomy has been performed on different areas: bottom left (n=12), lower right (n=9), and upper left (n=5).

Rhabdomyolysis occurs due to the stretching of the muscle sarcolemma due to pressure. When the sarcolemma is stretched, its permeability increases, and sodium, calcium, and water enter the cell. When the intracellular calcium level increases, proteolytic enzymes are activated,destroying the membrane (12). As a result, potassium, aldolase, phosphate, myoglobin, creatine kinase, lactate dehydrogenase, AST, ALT, and uric acid penetrate the bloodstream. These substances, whose levels rise in the blood, are responsible for toxic and fatal complications. Another mechanism that triggers rhabdomyolysis is ischemia. Ischemia occurs in skeletal muscle within 30 minutes, and edema and lysosome degranulation occur. Free radicals released in ischemia-reperfusion damage that develops during ischemia recovery also affect the pathogenesis of rhabdomyolysis (13). Increased intra-compartmental pressure due to trauma or edema disrupts the circulation in the muscle tissue. Impairment of blood supply causes ischemia, and edema tissue ischemia causes necrosis. ARF can be seen due to acidosis and myoglobinuria resulting from muscle tissue destruction (12 – 14).

The enzyme creatine kinase (CK) is found in striated muscles and is released into the circulation in case of muscle damage. Creatine kinase has two subtypes, CK–MM and CK–MB. In rhabdomyolysis, high concentrations of CK–MM enter the circulation. Serum CK concentration, mainly the CK–MM subtype, is the most sensitive indicator of muscle damage. The serum CK level begins to rise approximately 2 – 12 hours after muscle injury, peaks within 24 – 72 hours, then declines at a steady rate of 39% of the previous day's valueand returns to its normal value in 3 – 5days(15).Anion gap metabolic acidosis is increased s due to organic acids released from necrotic muscle cells, accumulated organic acids due to acute kidney injury (AKI), and lactic acid. Rhabdomyolysis usually leads to a faster increase in plasma creatinine than other causes of AKI. The BUN/creatinine ratio is often low in this patient group. Normal serum creatine kinase values are 25 – 175 U/L, but in cases with Crush syndrome, it usually rises above 15.000 IU/L. The peak value of creatine kinase can reach

100.000 IU/L. High creatine kinase values (especially CK>75.000 IU/L) are associated with acute kidney failure and mortality. The half-life of creatine kinase is 1.5 days, and the half-life of myoglobin is 3 hours. Also, creatine kinase is not removed by kidney or dialysis. Therefore, creatine kinase monitoring is more reliable than myoglobin monitoring for the treatment and prognosis of Crush syndrome (16). CK activity above 5.000 IU/L indicates severe muscle damage and is a potential indicator of kidney failure that may develop. Clinically, rhabdomyolysis can vary from asymptomatic to life-threatening clinical conditions such as cardiac arrhythmias, acute kidney injury, and disseminated intravascular coagulation(17). In our study, the median CK level at admission was 18.1U/L(range 1.8 – 330 U/L) and 208 U/L(range 1.5 – 919 U/L) at the final measurement, and this difference was statistically significant ($p<0.001$). On the contrary, CK–MB values at admission and final follow-up did not reach significance (97.2 U/L range 19.6 – 466 U/L versus 77.5 U/L range 18.5 – 432 U/L respectively, $p<0.070$).

The prominent local finding in patients is compartment syndrome. Other local findings are elaborated as 6P: pain, pressure, paresthesia, pulselessness, paresis, and pallor. Systemic findings differ according to the affected organ. Systemic findings are hypovolemic shock, hypotension, AKF, arrhythmia, heart failure, respiratory failure, infection, and sepsis. Oliguria or anuria may be seen in patients due to AKF(19).

Fasciotomy is a surgical incision in the fascia of the injured muscle to reduce intracompartmental pressure. There is no consensus on the indications for fasciotomy. Routinely performed fasciotomies in the early period can reduce the risk of necrotic muscle mass, the severity of kidney failure, peripheral neuropathy, and ischemic contracture, but they increase the risk of infection. Fasciotomy is a major risk factor for sepsis and should not be performed unless there are clear indications(20). Sepsis developed in 25% of patients who underwent fasciotomy in the Marmara Earthquake (21). During the Van Earthquake, 5 (23.8%) of 21 victims who underwent fasciotomy in Van Training and Research Hospital received treatment for sepsis (22). Fasciotomy should be considered in selected patients at risk of ischemia and gangrene, whose distal pulse cannot be obtained, whose intracompartmental pressure exceeds 50 mmHg, or whose pressure values between 30 and 50 mmHg do not tend to decrease for more than 6 hours.Guidelines recommend that amputation be limited to situations where a limb is unrecoverable or where injuries to the limb cause sepsis, systemic inflammation, or uncontrollable bleeding. İskit et al. reported that they performed fasciotomy in nine extremities of six children with compartment syndrome, who were admitted late after the third day, in whom distal pulses could not be detected. Still, they did not perform an amputation on patients (23). Donmez et al. reported performing fasciotomy in 15 of 20 pediatric patients and amputation in six extremities of four children(24).In our study, infection was observed in 38 children, and sepsis in only one child. Amputation has been performed on eight patients, and debridement on 17.

In the 1999 Marmara earthquake, child mortality was low compared to the general affected population. Only 18.7% of the population in the earthquake area were younger than ten years old, but only 1.9% of crush-related AKI patients were that age. This suggests that children may have died at the earthquake scene or been less affected by rhabdomyolysis complications due to their low body surface area (25). In a study by Jacquet et al., who systematically reviewed the literature on earthquake-related injuries in the pediatric population from 1950 to 2012 to provide recommendations for improving the reporting and classification of pediatric injuries in disasters, crush injuries were reported between 6.3% and 18.7% (26). It has been shown that the duration of being under the wreckage for children exposed to crush syndrome after the Marmara earthquake was also significantly longer than adults (23, 24). This finding

suggests that children are protected from trauma in narrow ranges. During the Guatemala earthquake, trauma risk and mortality were inversely proportional to age, except for very young children, probably because they slept with their parents (27). In the Iran-Bam earthquake, the percentage of crushed children and youth younger than 15 was significantly lower than the affected adult population in the same region (28). Less trauma, fractures, and chest injuries were recorded in children younger than ten in the China earthquake (29). Similar observations were also reported after the Japan Kobe earthquake (10).

Dönmez et al. stated that crushing syndrome of a large skeletal muscle mass, sensory and motor disturbances in the extremities, myoglobinuria and/or hematuria, and serum creatine kinase levels >1.000 U/L as diagnostic criteria for crush syndrome in the children they followed after the 1999 Marmara earthquake (24). Iskit et al. reported that they considered children with myoglobinuria or AKI (the cases with serum creatinine levels above 1.2 mg/dl or oliguria were accepted as AKI) with crush injury as crush syndrome (23). Oda et al.published the incidence of AKI in children with one, two, and three extremity injuries as 50.5%, 74.5%, and 100%, respectively. In the same study, they indicated that they observed AKI only in 14.3% of children with one extremity injury and in 85.7% of children with multiple extremity injuries and that the number of affected extremities is an important factor in determining the severity of crush syndrome (30). In our study, intubation and mechanical ventilation were performed on one patient each, respectively. Regarding biomarkers and laboratory parameters, there was a statistically significant difference between the two groups in the baseline WBC, uric acid, potassium values, d final WBC, albumin, and calcium measurements ($p<0.05$).Children with multiple extremity involvementhad significantly higher initiallaboratory measurement levels, while this was vice versain those with single extremity involvement, as they presented higher values in the final measurements.

CONCLUSION

As earthquakes are unpredictable, it is necessary to be prepared. The high creatine kinase levelsmight indicate the severity of muscle damage in Crush syndrome. Elevated creatine kinase could be used to indicate in-hospital mortalityin these patients. Early assessment of compartment pressure can eliminate the risk of amputation. Rapid diagnosis and aggressive fluid resuscitation in the emergency department can prevent acute kidney injury or failure.

Ethical Declaration

All procedures were followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. As this was a retrospective research no informed consent has been obtained from participants.

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Abbreviations

AKF : Acute kidney failure
AKI : Acute kidney injury

ALT : Alanine transaminase
APTT : Activated partial thromboplastin time
AST : Aspartate transaminase
BUN : Blood urea nitrogen
CK : Creatine kinase
CRP : C – reactive protein
DIC : Disseminated intravascular coagulation
Hb : Hemoglobine
HCT : Hematocrite
ICU : Intensive care unit
INR : International normalized ratio
LDH : Lactate dehyrogenase
MV : Mechanical ventilation
PLT : Platelets
PT : Prothrombine time
SPSS : Statistical Package for the Social Sciences
WBC : White blood cells

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Biochemical and Histopathological Evaluation of The Effect of Thiamine Pyrophosphate on Favipiravir-İnduced Degenerative Corneal and Scleral Damage in Rats

Tiamin Pirofosfatın Sıçanlarda Favipiravir ile İndüklenen Dejeneratif Kornea ve Skleral Hasarına Etkisinin Biyokimyasal ve Histopatolojik Değerlendirmesi

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Abstract

Introduction: Favipiravir causes ocular toxicity at high doses. Thiamine pyrophosphate (TPP) therapy can prevent ocular damage by reversing oxidative damage.
Objective: To investigate the ocular effect of favipiravir in rats and determine the protective effect of thiamine pyrophosphate (TPP) against the possible ocular toxicity of favipiravir.
Method: The rats were randomly divided into three groups; healthy control (HC), favipiravir administered (FAV), and TPP + favipiravir administered (TFAV). In the TFAV group, TPP was intraperitoneally injected at a dose of 25 mg/kg. In the HC and FAV groups, distilled water was applied as a solvent. One hour later, favipiravir was administered to the FAV and TFAV groups at 200 mg/kg orally by gavage twice a day. TPP was injected once a day. This procedure was repeated for one week. All rats were sacrificed under anesthesia, and the biochemical parameters and histopathological levels were analyzed.
Results: It was determined that the FAV group had higher blood MDA levels ($p<0.001$) and lower tGSH, SOD, and CAT levels ($p<0.001$) than the other groups. MDA levels of HC and TFAV groups were similar ($p=0.407$). It also inhibited the reduction in TPP, tGSH, SOD, and CAT ($p<0.001$). There was no significant difference between HC and TFAV groups regarding tGSH and CAT ($p>0.05$). In the histopathological examinations, severe collagen fiber degeneration and moderate hyperemia were observed in the corneal and scleral tissues in the FAV group.
Conclusion: The findings of the study showed that favipiravir caused damage to the cornea and sclera tissue through oxidative damage and TPP reduced this damage. Our study results suggest that TPP may be beneficial in Favipiravir-induced ocular toxicity.

Keywords: Favipiravir, Ocular Toxicity, Oxidative Stress, Thiamine Pyrophosphate.

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Özet

Giriş: Favipiraviryüksek dozlarda oküler toksisiteye neden olmaktadır. Tiamin pirofosfat (TPP) tedavisi oksidatif hasarı tersine çevirerek oküler hasarı önleyebilir.
Amaç: Favipiravirin sıçanlarda oküler etkisini araştırmak ve favipiravirin olası oküler toksisitesine karşı TPP koruyucu etkisini belirlemek.
Yöntem: Sıçanlar rastgele üç gruba ayrıldı; sağlıklı kontrol (HC), favipiraviruygulanan(FAV) ve TPP + favipiravir (TFAV)uygulanan. TFAV grubuna TPP intraperitoneal olarak 25 mg/kg dozunda enjekte edildi. HC ve FAV gruplarında çözücü olarak distile su uygulandı. Bir saat sonra FAV ve TFAV gruplarına günde 2 kez 200 mg/kg oral sonda ile favipiravir uygulandı. TPP günde bir kez enjekte edildi. Bu prosedür bir hafta boyunca tekrarlandı. Tüm sıçanlar anestezi altında sakrifiye edildi ve biyokimyasal parametreler ve histopatolojik seviyeleri analiz edildi.
Bulgular: FAV grubunun diğer gruplara göre kan MDA düzeylerinin daha yüksek ($p<0.001$), tGSH, SOD ve CAT düzeylerinin daha düşük olduğu ($p<0.001$) belirlendi. HC ve TFAV gruplarının MDA düzeyleri benzerdi ($p=0,407$). Ayrıca TPP, tGSH, SOD ve CAT'deki azalmayı da inhibe etti ($p<0.001$). tGSH ve CAT açısından HC ve TFAV grupları arasında anlamlı fark yoktu ($p>0,05$). Histopatolojik incelemelerde FAV grubunda kornea ve sklera dokularında ileri derecede kollajen lif dejenerasyonu ve orta derecede hiperemi gözlendi.
Sonuç: Çalışmanın bulguları, favipiravirin oksidatif hasar yoluyla kornea ve sklera dokusunda hasara neden olduğunu ve TPP'nin bu hasarı azalttığını gösterdi. Çalışma sonuçlarımız, TPP'nin favipiravirin neden olduğu oküler toksisitede faydalı olabileceğini düşündürmektedir.

Anahtar Kelimeler: Favipiravir, Oküler Toksisite, Oksidatif Stres, Tiamin Pirofosfat.

INTRODUCTION

Favipiravir is a purine nucleoside precursor antiviral drug that competitively inhibits the RNA-dependent RNA polymerase (RdRp) enzyme (1). It is converted to its active form, favipiravir-ribofuranosyl-50-triphosphate metabolite, through phosphoribosylation and phosphorylation in tissues (2). Favipiravir was first manufactured by the Japanese pharmaceutical company Fujifilm Toyama Chemical Co. Ltd. (3). It was initially found to be effective against the influenza virus in vitro (4).However, evidence from in vitro and clinical studies has shown that favipiravir is also a promising drug against a broad spectrum of RNA viruses (5). It has been determined that favipiravir is effective against many RNA viruses, such as Ebola, norovirus, and enterovirus.1 In addition to other RNA viruses, such as the Ebola virus, a few studies have also reported the effects of favipiravir against rhinovirus and respiratory syncytial virüs (6).

It has been suggested to use high doses of favipiravir in infections of COVID-19, Ebola, and similar viruses, and it has been stated that these viruses are sensitive to high doses of favipiravir (7). However, favipiravir can have toxic effects at high doses (8), which can be seen in the form of diarrhea, nephrotoxicity, increased serum uric acid and transaminase levels, decreased white blood cell and neutrophil levels, nausea, vomiting, abdominal pain, skin rash, itching, delirium, hallucinations, and convulsions (9,10). Side effects such as blurred vision and blue light reflection have been reported after the use of favipiravir in the treatment of COVID-19 (11). Favipiravir has also been shown to cause oxidative liver damage by increasing the level of malondialdehyde (MDA) formed by peroxidation of membrane lipids and decreasing the levels of endogenous oxidants, such as catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH) (12).

The global increase in cases of COVID-19 has led to the need to discover and develop new therapeutics with superior efficacy to treat this disease. Thiamine pyrophosphate (TPP) is the active metabolite of thiamine in the body. TPP participates as a cofactor in the reactions of enzymes that maintain cell redox state through the synthesis of glutathione and nicotinamide

adenine dinucleotide phosphate (NADPH) (13). It has been stated that TPP protects retinal tissue by preventing the increase in MDA from ethanol-induced oxidative damage to the retina, as well as the decrease in tGSH (14). In addition, it has been suggested that TPP suppresses the formation of diabetic retinopathy by preventing the decrease of SOD and other enzymatic antioxidant systems (15).

In the literature review, no experimental study was found regarding the effects of favipiravir on eye tissue. Therefore, in the current study, we aimed to investigate the ocular effect of favipiravir biochemically and histopathologically and determine the protective effect of TPP against the possible ocular toxicity of favipiravir.

METHOD

Animals

In the current study, 18 male albino Wistar rats (265-272 grams) were included. Animals were obtained from Experimental Animals Application and Research Center of our university. Before the experiment, the rats were kept at the appropriate temperature (21-23°C), 12 hours of light-dark cycle, and fed ad libitum. This research followed according to the Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research. This research also followed the Institute of Laboratory Animal Resources Guide for the Care and Use of Laboratory Animals. Ethical approval was obtained from the Animal Experiments Local Ethics Committee of our university for the procedures to be applied to rats (meeting date: 28.07.2022, decision no: 07/35).

Chemical Substances

Thiopental sodium was obtained from IE Ulagay (Turkey), favipiravir from a training and research hospital affiliated with the Turkish Ministry of Health, and an injectable form of TPP from Biopharma (Russia).

Experimental Groups

Healthy control (HC), favipiravir administered (FAV), and TPP + favipiravir administered (TFAV) groups were formed from rats by randomization, with six animals in each group.

Experimental Procedure

For the experiment, the animals in the TFAV (n = 6) group were injected with TPP (25 mg/kg) intraperitoneally. In the HC (n = 6) and FAV (n = 6) groups, distilled water was given. One hour after administration of TPP and distilled water, favipiravir (200 mg/kg) was given orally twice a day to rats in FAV and TFAV groups. TPP was injected once a day. This procedure was repeated for one week. At the end of a week, blood samples were taken from the tail veins of the animals for MDA, tGSH, SOD, and CAT analysis, and then euthanized with 50 mg/kg thiopental sodium, and the eyeballs were removed. The cornea, sclera, and retinal tissues of the eye were analyzed histopathologically. The obtained data were compared between the groups.

Biochemical Analyses

MDA (µmol/g protein), GSH (nmol/g protein), and SOD (u/mg protein) in blood samples were measured using the commercial enzyme-linked immunosorbent assay (ELISA) kits for experimental animals, and each analysis was performed according to the kit instructions (product number: 706002, 703002, and 10009055, respectively, Cayman Chemical

Company). CAT (u/mg protein) determination was made according to the method proposed by Goth (16). Protein determination was undertaken spectrophotometrically at 595 nm according to the Bradford method (17).

Histopathological Examination

Eye tissues were fixed in a 10% formalin solution. After routine tissue follow-up, 5 µm sections were obtained and stained with hematoxylin-eosin. Prepared sections were analyzed histopathologically under the light microscope (Olympus BX 51, Japan). Photos were taken with a digital camera (Olympus DP 71). Histopathological findings, which were determined semi-quantitatively in the evaluation, were evaluated as absent (0), mild (1), moderate (2), and severe (3).

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis and $p<0.05$ was considered significant. The data of the study were expressed as mean value ± standard deviation. Statistical analysis for biochemical data was performed with a one-way ANOVA test. Afterward, the Tukey HSD test was applied. Since the histopathological data were ordinal, they were preferred with the Kruskal-Wallis test, which is a non-parametric method, and then a pairwise comparison was made with Dunn's test.

RESULTS

Biochemical Results

As seen in Figure 1 and Table 1, favipiravir administration increased MDA levels compared to the HG group ($p<0.001$). The addition of TPP to favipiravir appeared to inhibit this increase ($p<0.001$) and approximate the MDA data of the TFAV group to those of healthy animals ($p=0.407$). tGSH, SOD, and CAT levels obtained from animals in the FAV group were found to be statistically significantly lower than those of the HCand TFAV groups ($p<0.001$). With TPP application, tGSH and CAT levels were close to healthy animals ($p>0.05$), while the difference in SOD levels was significant ($p=0.003$).

Table 1. Analysis Results of Biochemical Variables

Variables	HC	FAV	TFAV	HC vs. FAV	HC vs. TFAV	FAV vs. TFAV	F/p
	X ±SD (mean±standard deviation)			*p* values			
MDA	1.13±0.13	4.60±0.37	1.33±0.26	<0.001	0.407	<0.001	304.658/<0.001
tGSH	3.56±0.13	1.58±0.17	3.27±0.26	<0.001	0.050	<0.001	182.645/<0.001
SOD	8.65±0.25	4.20±0.57	7.69±0.35	<0.001	0.003	<0.001	192.009/<0.001
CAT	6.36±0.11	3.50±0.21	5.98±0.41	<0.001	0.066	<0.001	192.696/<0.001

HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group; MDA: Malondialdehyde; tGSH: Total Glutathione; SOD: Superoxide Dismutase; CAT: Catalase.

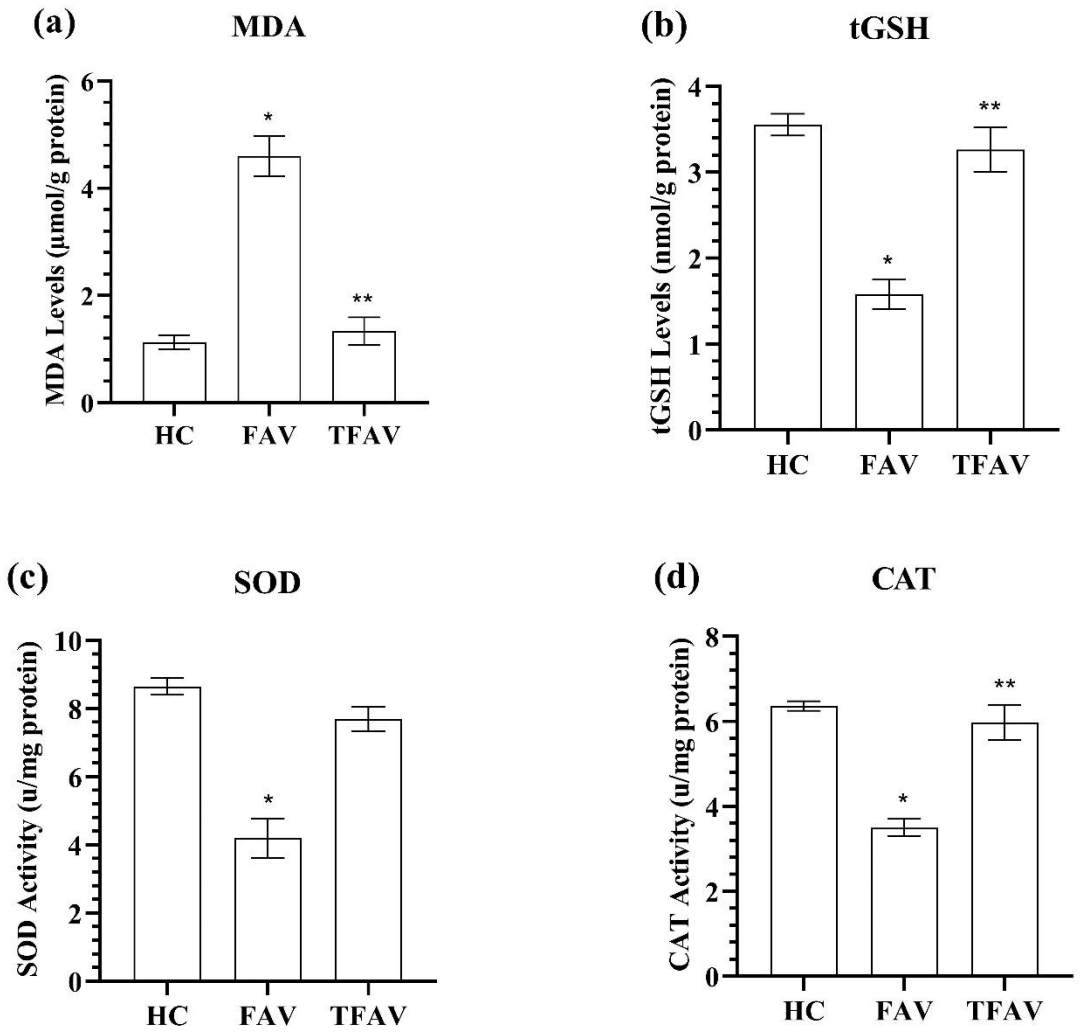

Figure 1. MDA, tGSH, SOD, and CAT values of eyes samples taken from study groups. Bars are mean±SD, n=6. (a), MDA levels; (b), tGSH levels; (c), SOD activity; (d), CAT activity. * means p<0.001 compared to HC and TFAV groups; ** means p>0.05 compared to HC group. HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group; MDA: Malondialdehyde; tGSH: Total Glutathione; SOD: Superoxide Dismutase; CAT: Catalase.

Histopathological Results

The histopathological analysis results of the groups are summarized in Table 2.

Table 2. Analysis Results of Scoring.Histopathological

Variables		HC	FAV	TFAV	HC vs. FAV	HC vs. TFAV	FAV vs. TFAV	KW/p
		X ±SD (mean±standard deviation)			*p* values			
Cornea	Degeneration	0	2.67±0.52	1.00±0.63	<0.001	0.240	0.110	14.775/0.001
	Hyperemia	0	0	0	-	-	-	-
Sclera	Degeneration	0	2.83±0.41	0.83±0.41	<0.001	0.262	0.079	15.540/0.001
	Hyperemia	0	2.17±0.41	0	<0.001	1.000	<0.001	16.615/0.001
Retina	Degeneration	0	0	0	-	-	-	-
	Hyperemia	0	0	0	-	-	-	-

HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group.

No pathological findings were found in the corneal, scleral, and retinal tissues of the animals in the HC group (Figure 2a-c).

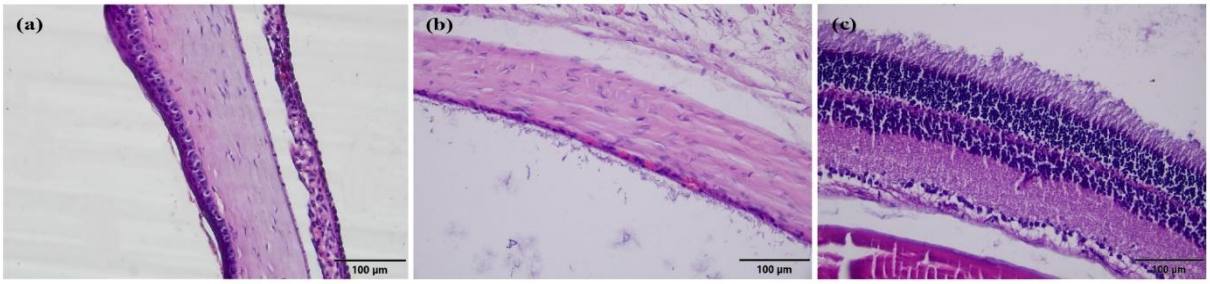

Figure 2. Histopathological appearance of the HC group (HxE). a- Normal appearance of the corneal tissue. b- Normal appearance of scleral tissue. c- Normal appearance of retinal tissue. HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group.

However, severe collagen fiber degeneration was observed in the corneal and scleral tissue of the FAV group (Figure 3a,b). In addition, favipiravir was found to cause moderate hyperemia in the scleral tissue (Figure 3b). Microscopic pathological findings were not present in the retinal tissue of the animals treated with favipiravir (Figure 3c).

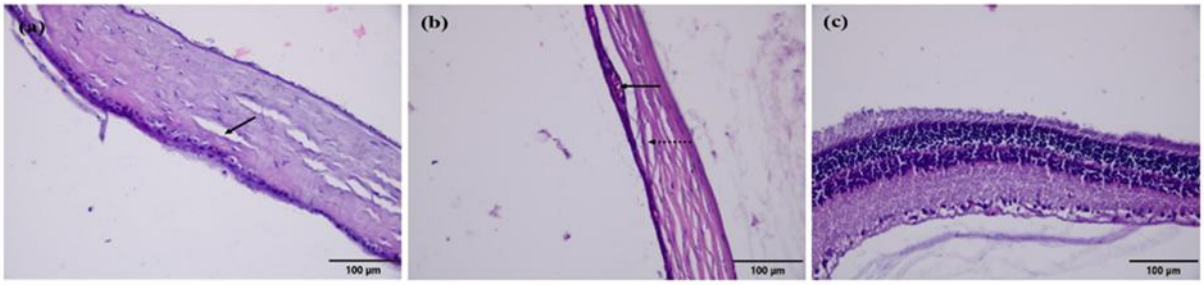

Figure 3. Histopathological appearance of the FAV group (HxE). a- Severe collagen fiber degeneration (arrow) and decrease in collagen fiber density in the corneal tissue. b- Severe collagen fiber degeneration (arrow) and moderate hyperemia (dashed arrow) in scleral tissue. c- Normal appearance of retinal tissue. HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group.

There was mild collagen fiber degeneration in the cornea and sclera tissue of the animals in the TFAV group. No hyperemia was observed in the cornea and sclera tissues. (Figure 4a, b). In addition, the retinal tissue of the TFAV group had a normal histological appearance (Figure 4c).

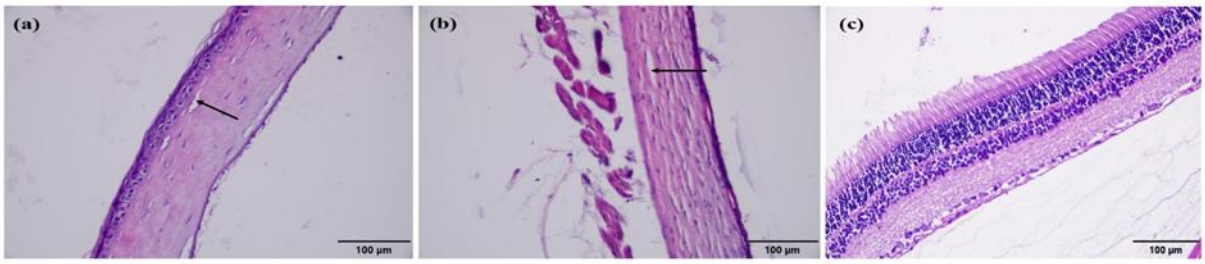

Figure 4. Histopathological appearance of the TFAV group (HxE). a- Mild collagen fiber degeneration (arrow) finding in the corneal tissue. b- Mild collagen fiber degeneration (arrow) in scleral tissue. c- Normal appearance of retinal tissue. HC: Healthy Control; FAV: Favipiravir Group; TFAV: Thiamine Pyrophosphate+Favipiravir Group.

DISCUSSION

In the current study, the effect of TPP on favipiravir-induced oxidative corneal and scleral damage was investigated biochemically and histopathologically. Our biochemical findings showed that favipiravir significantly increased the amount of MDA, whereas it significantly decreased the levels of endogenous antioxidants, namely tGSH, SOD, and CAT.

The main reason why we measured the MDA level to evaluate ocular damage caused by favipiravir is that MDA is one of the most important indicators of lipid peroxidation (LPO). Many studies have reported that in damaged corneal and scleral tissues, there is an increase in the level of reactive oxygen radicals (ROS) and oxidative stress products, such as MDA (18,19). MDA plays a role in the continuation of oxidative cell damage after LPO (20). MDA also exerts its toxic effect by causing the cross-linking of cell membrane components and inactivating receptors and enzymes in membranes (21). However, to our knowledge, in the literature, there is no experimental study that has investigated the toxic effect of favipiravir on ocular tissue. However, Kara et al. reported that favipiravir triggered oxidative damage by causing an increase in MDA levels in liver and kidney tissues (12). Analysis results of the current study and literature information suggest that as a result of favipiravir administration, the prooxidant/antioxidant balance shifts in favor of prooxidants in various tissues.

Recent experimental studies have shown that the toxic effects of various drugs can be reduced by treatment with substances and antioxidants that prevent the formation of ROS (22,23). Therefore, in our study, we investigated the effect of TPP, which is known to have antioxidant properties, against possible favipiravir-related ocular toxicity. TPP is a cofactor of enzymes that play a role in maintaining the cellular redox state by synthesizing NADPH and GSH and showing antioxidant properties (13). The findings obtained from the current study revealed that the administration of TPP to the rats significantly reduced the increase in MDA caused by favipiravir. The role of TPP therapy has been previously investigated in certain ocular diseases, and related data support our findings. Çinici et al. determined that TPP exhibited a protective effect by inhibiting MDA in ethambutol-induced ocular toxicity (14). Similarly, in another study, it was reported that the increase in the amount of MDA in the retinal tissues of rats associated with hyperglycemia was significantly inhibited by TPP administration (15). Our experimental results and information obtained from previous studies show that TPP

protects ocular tissue from the toxic effect of favipiravir by creating an antioxidant effect on ROS.

The impairment of the oxidant/antioxidant balance and oxidative stress damage is among the most implicated mechanisms in the etiopathogenesis of ocular toxicity caused by various drugs (23,24). Therefore, in our study, we measured tGSH levels in blood samples taken from the rats to evaluate favipiravir-induced oxidative damage. GSH is one of the important indicators of antioxidant capacity and is known to protect tissues against oxidative stress (25). It is one of the most well-known important antioxidants in living tissues. GSH, catalyzed by active glutathione peroxidase, reacts with hydrogen peroxide and organic peroxides to detoxify and protect cells from ROS damage (26). Although there are many studies documenting a decrease in the amount of GSH in the presence of oxidative damage in ocular tissue (23,24), there is no study in the literature that associates favipiravir-induced ocular damage with decreased GSH. The decrease in the amount of endogenous tGSH in serum samples of rats administered favipiravir in the current study supports the literature.

Other enzymatic antioxidants that were observed to be decreased in the serum samples of the rats as a result of favipiravir administration were SOD and CAT. SOD catalyzes the conversion of superoxide to hydrogen peroxide and molecular oxygen, thereby inhibiting LPO (27). As a result of this reaction, hydrogen peroxide is formed, which is detoxified by the CAT enzyme (28). Therefore, in our study, we decided to examine the SOD enzyme together with the CAT enzyme to prevent the destructive effect of ROS. Although it has been reported in the literature that a decrease in enzyme activities, such as SOD and CAT is associated with ocular oxidative damage (14,15,22,29), no study has associated favipiravir-induced ocular damage with endogenous antioxidant enzyme activities. However, it is known that xanthine oxidase, which is formed as a result of the metabolism of favipiravir, is a major source of free radicals, and there are many studies documenting that xanthine oxidase causes ROS production, which then results in a decrease in antioxidants in tissues (12,30). In a recent study, it was reported that following favipiravir administration, there was a decrease in SOD, CAT, GSH, and glutathione peroxidase levels, as well as an increase in MDA levels in liver and kidney tissues (12). All these literature data support our findings.

In this study, it was observed that TPP inhibited the decrease in tGSH, SOD, and CAT levels along with the increase in favipiravir-related MDA. As our experimental results revealed, the oxidant-antioxidant balance was impaired in the FAV group and oxidants became dominant, but this balance was maintained in the group that was additionally administered TPP. In the current literature, there are limited studies on the effect of TPP on oxidative stress in ocular tissue (14,15). It has been reported that TPP protects ocular tissue against oxidative damage induced by ethambutol and hyperglycemia (14,16). Our findings are consistent with previous reporting the antioxidant effect of TPP.

The biochemical findings of our study were supported by histological findings. The results of our histological findings showed that the FAV group had severe collagen fiber degeneration in the corneal and scleral tissues and moderate hyperemia in the scleral tissue. We consider that this histopathological damage associated with favipiravir is related to the increase in oxidant parameters. These findings are in line with the case report of Doran et al., who observed blurred vision and blue light reflection after favipiravir treatment in COVID-19 cases (11). However, in our study, treatment with TPP significantly suppressed favipiravir-induced corneal and scleral degeneration and hyperemia. These findings are also consistent with previous studies reporting that TPP prevented ocular toxicity caused by ethambutol and retinopathy damage caused by hyperglycemia (14,15).

CONCLUSION

In this study, favipiravir caused an increase in oxidants and a decrease in antioxidants in blood serum, and TPP significantly inhibited the favipiravir-related oxidant increase and antioxidant decrease. Our histopathological findings revealed that the retinal tissue was not affected by favipiravir, but significant histopathological damage developed in the corneal and scleral tissues of the rats. TPP alleviated favipiravir-related corneal and scleral damage. To our knowledge, this is the first study to show that favipiravir-induced ocular toxicity is associated with increased oxidative damage in a rat model. Furthermore, treatment with TPP was determined to reverse this oxidative damage and prevent ocular damage. Our experimental results suggest that TPP may be useful in the treatment of favipiravir-related ocular damage. Further studies are needed to elucidate the mechanisms through which TPP acts. It is important to directly measure and evaluate oxidant and antioxidant parameters in corneal, scleral, and retina tissues.

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The Effects of Lockdown on the Severity of Symptoms of Attention Deficit Hyperactivity Disorder and Disruptive Behavior Disorders and on Children/Adolescents' Ability to Cope with Stress

Karantina Döneminin Çocuk ve Ergenlerin Dikkat Eksikliği Hiperaktivite Bozukluğu ve Yıkıcı Davranış Bozukluklarının Belirti Şiddeti ve Stresle Baş Etme Becerileri Üzerindeki Etkisi

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Abstract

Introduction and Objective: The aim is to examine changes in the severity of symptoms during the lockdown period in patients diagnosed with attention deficit hyperactivity disorder (ADHD) and Disruptive Behavior Disorders (DBD), and to determine the relationship between the methods of coping with the stress experienced by the children and the severity of ADHD and DBD.

Method: 92 patients, between the ages of 6-18, who were diagnosed with ADHD included in the study. Sociodemographic data form and the Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale were given to parents, the Coping Styles of Stress Scale was given to children.

Results: It was found that ADHD, Oppotional Defiant Disorder (ODD), and Conduct Disorder (CD) scores decreased significantly, compared to before the pandemic. There wasn't a significant difference between pandemic-related features and ADHD, ODD, and CD scores. A significant relationship was not observed between stress-coping methods and ADHD and CD scores and as ODD scores increased, the rate of using the submissive approach increased.

Conclusion: Adaptation to acute changes such as a pandemic can be challenging for children and adolescents. During these processes, especially children and adolescents diagnosed with ADHD are at risk for developing additional mental problems. Evaluating the stress coping methods of patients diagnosed with ADHD and DBD and their parents who apply to outpatient clinics in interviews and supporting them to develop healthy coping methods are important issues both during the stressful situation and in terms of providing psychological resilience against subsequent stresses.

Keywords: Attention Deficit Hyperactivity Disorder, Disruptive Behavior Disorder, Coping Strategies, COVID-19 Pandemic, Lockdown.

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Özet

Giriş ve Amaç: Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) ve Yıkıcı Davranış Bozuklukları (YDB) tanısı konmuş hastaların karantina dönemindeki semptom şiddetindeki değişikliğin incelenmesi ve DEHB ve YDB'nin şiddeti ile çocuklar tarafından yaşanan stresle baş etme yöntemleri arasındaki ilişkinin belirlenmesi amaçlanmaktadır.
Yöntem: Çalışmaya DEHB tanısı almış 6-18 yaş arası 92 hasta dahil edilmiştir. Ebeveynlere sosyodemografik veri formu ve Turgay Çocuk ve Ergenlerde Davranım Bozuklukları için DSM-IV'e Dayalı Tarama ve Derecelendirme Ölçeği, çocuklara ise Stresle Başa Çıkma Tarzları Ölçeği verilmiştir.
Bulgular: Pandemi öncesine göre DEHB, Karşıt Olma Karşı Gelme (KOKGB) ve Davranım Bozukluğu (DB) puanlarının anlamlı olarak düştüğü saptanmıştır. Pandemi ile ilişkili özellikler ile DEHB, KOKGB ve DB puanları arasında anlamlı bir fark bulunmamıştır. Stresle başa çıkma yöntemleri ile DEHB ve DB puanları arasında anlamlı bir ilişki gözlenmemiş ve KOKGB puanları arttıkça boyun eğici yaklaşımı kullanma oranının arttığı saptanmıştır.
Sonuç: Pandemi gibi akut değişikliklere uyum çocuk ve ergenler için zorlayıcı olabilmektedir. Bu süreçlerde özellikle DEHB tanılı çocuk ve ergenler ek ruhsal sorunlar geliştirmek açısından risk altındadır. Polikliniklere başvuran DEHB ve YDB tanılı hastaların ve ebeveynlerinin stresle başa çıkma yöntemlerinin görüşmelerde değerlendirilmesi ve sağlıklı baş etme yöntemleri geliştirmeleri açısından desteklenmesi hem stres yaratan durumun yaşandığı süreçte hem de sonraki streslere karşı psikolojik dayanıklılık sağlanabilmesi açısından önemli konulardır.

Anahtar Kelimeler: Dikkat Eksikliği Hiperaktivite Bozukluğu, Yıkıcı Davranış Bozukluğu, Baş Etme Yöntemleri, COVID-19 Pandemisi, Kısıtlama.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children. Attention problems, hyperactivity, and impulsivity is observed in clinical evaluation (1). ADHD has a negative impact on many aspects of children's lives, particularly their self-esteem, academic performance, relationships and emotions (2,3). In addition to genetic factors, environmental factors also influence the severity of ADHD symptoms. While symptoms are less likely to be observed in unfamiliar or quiet environments, factors that increase arousal, such as high visual stimulation, noisy environments and crowded classrooms, can increase impulsivity and inattention (4).

The COVID-19 pandemic is a worldwide health issue, and measures such as the suspension of face-to-face education, restrictions on social life and lockdowns have been implemented in our country since March 2020 to prevent the spread of infection. The long-term isolation experienced as a result of this situation and the uncertainty caused by the pandemic have had a negative impact on people's mental health. Increases in depression, post-traumatic stress disorder, sleep disorders and domestic violence have been observed (5,6). Studies have shown that the pandemic has led to a deterioration in the mental health of the pediatric population due to the suspension of face-to-face education, the implementation of social distancing policies, the reduction of outdoor activities and social interaction, and the increase in time spent online (7,8). In addition to academic learning, continued face-to-face education allows children and adolescents to develop the social skills necessary for their mental health, to maintain contact with their teachers and classmates, and to receive emotional support from their environment (9,10). However, switching to distance learning as a result of the pandemic has isolated children, increased feelings of loneliness and negatively affected their mental health (11,12).

The aim of this study is to investigate whether there is a change in the symptom severity in children and adolescents diagnosed with ADHD and disruptive behavior disorders (DBD) in our department before the pandemic, during the implementation of the COVID-19 pandemic

precautions, and to determine whether there is an association between the children's coping mechanisms with stress and the ADHD and DBD symptom severity.

METHOD

Study approval was obtained from Kocaeli University Clinical Research Ethics Committee under the reference number GOKAEK-2021/4.08 on 18 February 2021. Patients and their families were asked to complete informed consent forms, which were prepared separately for parents and children.

Design and Sample

This was a cross-sectional survey carried out at a university hospital in Kocaeli, Turkey. Patients were taken into the study from the department of child/adolescent psychiatry. All patients who presented to the Child/Adolescent Psychiatry Department of our hospital in the year before the start of the pandemic between the ages of 6-18 years, and diagnosed with ADHD and had the Turgay DSM-IV-based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S), which is routinely administered in our department and completed by parents. Patients with neurological disorders, organic brain damage, major depressive disorder, anxiety disorder, and intellectual disability were not included in the study. Patient files were screened according to the inclusion criteria and these patients were contacted by phone and informed about the study. Forms were given to the patients who agreed to participate in the study and their parents, and they were asked to fill them out online or during outpatient clinic visits. Some of the data obtained in the study were used in a study titled " Being a Child with ADHD, and Parent of them during the Pandemic Period" and the results obtained were sent to another scientific journal for publication.

Data Collection Process

Sociodemographic Data Form

This form, prepared by the researchers, asked about the patient's age, sex, who the patient lived with, what medication the patient was taking, the parents' age, education and health status, and pandemic's effects on the child and the family, was given to parents.

Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S)

The scale was routinely given to parents during our interviews. The scale was developed by Atilla Turgay (13) in 1995. In the scale, 9 questions assess Attention Deficit Disorder (AD), 9 questions assess Hyperactivity-Impulsivity (HI), 8 questions assess Oppositional Defiant Disorder (ODD), and 15 questions assess Conduct Disorder (CD). The validity and reliability of the scale, which consists of 41 questions in Turkish, were ensured by Ercan et al (14). Each item is scored as "0=none, 1=a little, 2=more than a little, 3=a lot". ADHD, ODD and CD were diagnosed using the scale in conjunction with clinical interviews. A minimum of 12 points for ADHD subtypes, 8 points for ODD and 6 points for DD were considered sufficient for diagnosis using the scale. The scale is routinely administered at the first outpatient clinic visit for children suspected of having ADHD. Parents of children and adolescents were completed the scale again during the pandemic.

The Coping Mechanisms for Stress Scale (CSSS)

The scale was administered to children to determine how they were coping with the traumatic pandemic and the process of restriction. The interviewer helped young children who had difficulty reading or understanding the questions to complete the forms. The scale was developed by Şahin and Durak (15) based on the Coping Mechanisms Inventory developed by Folkman and Lazarus (1980) (16) to assess individuals' coping mechanisms with stress. The scale consists of a total of 30 4-point Likert items and a total of five sub-dimensions: Self-Confident Approach (SCA), Optimistic Approach (OA), Helpless Styles Approach (HSA), Submissive Approach (SA) and Social Support Seeking Approach (SSSA).

Statistical Analyses

The data collected were analyzed using the IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program. The Kolmogorov-Smirnov test was used to evaluate the suitability of the normal distribution. Normally distributed numerical variables are represented by mean +/- standard deviation, non-normally distributed numerical variables are represented by median (25.-75. percentiles), and categorical variables are represented by frequency (percentiles). The Wilcoxon Test was used to compare before and after pandemic T-DSM-IV-S subscale median scores. Spearman Correlation Analysis was used for correlation between coping mechanisms for stress and ADHD subtypes, ODD, and CD. $p<0.05$ was considered sufficient for statistical significance.

RESULTS

In the study group consisting of 92 patients, 22 were female (23.9%) and 70 were male (76.1%). The mean age of the group is 12.12±2.44 years, and 14.1% of the group attended primary school, 56.5% of the group attended secondary school and 29.4% of the group attended high school.

The mean age of the mothers was 39.98±5.28 years and the majority of them were high school graduates (35.9%) and housewives (76.1%); 92.4% (n:85) had no mental illness and 90.2% (n:83) had no physical illness.

The mean age of the fathers was 42.34±6.40 years and 43.5% of them were high school graduates, 97.8% were employed, 96.7% (n:89) had no mental illness, and 88% (n:81) had no physical illness.

Looking at the impact of the pandemic on the lives of children in the group, 69.9% of the children reported never or rarely meeting their friends over the internet/phone and 78.8% reported not following online lessons. Other effects are shown in Table 1.

When examining how symptoms of ADHD and DBD changed with the pandemic, it was found that ADHD, ODD and CD scores decreased significantly compared to before the pandemic (Table 2).

Table 1. Effects of the Pandemic Process on the Lives of Children with ADHD

Groups	Features	N	Percentage (%)
How children spend time at home during lockdown	Studying	46	50
	Spending time on the internet	40	43.5
	Doing activities with the family	3	3.3
	Talking or doing activities with friends	3	3.3
Frequency of the childrens' communication with friends over the internet/phone	Never – Rare	64	69.6
	Frequent - Very often	28	30.4
Childrens' follow-upstatus of online lessons	No	72	78.3
	Yes	20	21.7
Change in the childrens' sleep pattern	Same	48	52.2
	Hours have changed	30	32.6
	Total sleep time increased	7	7.6
	Total sleep time decreased	7	7.6
How was the change if the sleep time has changed	Late bedtime	24	54.5
	Irregular bedtime	19	43.2
	Early bedtime	1	2.3
Childrens' history of contracting Covid-19	No	79	85.9
	Yes	13	14.1

ADHD: Attention-Deficit Hyperactivity Disorder

Table 2. T-DSM IV-S Median Scores and Percentiles Before and After the Pandemic

T-DSM IV- S Subscale Scores	Before Pandemic	After Pandemic	P
	Median (25. - 75. percentil)	**Median (25. - 75. percentil)**	
ADHD-AD	13.50 (9.00-17.00)	10.00 (6.00-15.00)	**<0.001***
ADHD- HI	11.50 (6.00-18.50)	7.00 (3.00-13.00)	**<0.001***
ADHD- total score	25.00 (17.00-34.75)	20.00 (10.00-25.00)	**<0.001***
ODD	7.00 (4.00-14.00)	6.00 (2.00-11.00)	**0.006***
CD	1.00 (0.00-3.00)	0.00 (0.00-2.00)	**0.002***

*p<0.05, Instatistical analysis, Wilcoxon-T test was used.
AD: Attention-Deficit, HI: Hyperactivity-Impulsivity, ADHD: Attention-Deficit Hyperactivity Disorder, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder

In females, HI and total ADHD scores decreased significantly after the pandemic, whereas the decrease in AD, ODD and CD scores was not significant. In males, AD, HI and total ADHD, ODD and CD scores were found to decrease significantly ($p<0.05$) after the pandemic.

In the 7-11 age group, AD, HI, total ADHD and CD scores decreased significantly compared to the pre-pandemic period, and the decrease in ODD score was not significant. In the 12-18 age group, AD, HI, total ADHD, ODD and CD scores decreased significantly compared to the pre-pandemic period ($p<0.05$).

23 (25%) of the children diagnosed with ADHD included in the study were not using medication, 56 (60.9%) of those using medication were using methylphenidate, 9 (9.8%) were

using atomoxetine, 3 (3.3%) were using atomoxetine and methylphenidate. AD, HI, total ADHD, ODD and CD scores decreased significantly in children taking medication compared to those not taking medication ($p<0.05$). The AD, HI, total ADHD and CD scores of the non-medicated group decreased significantly compared to the pre-pandemic period, but the decrease in ODD scores was not significant.

Table 3. Correlation Between Stress Coping Styles and ADHD Subtypes

T-DSM IV- S Subscale Scores	Coping Styles of Stress Scale				
	SCA	**SA**	**HSA**	**OA**	**SSSA**
	r (p)	**r (p)**	**r (p)**	**r (p)**	**r (p)**
ADHD-AD	-0.241 (0.054)	0.263 **(0.034*)**	0.269 **(0.030*)**	-0.068 (0.592)	-0.034 (0.790)
ADHD- HI	-0.303 **(0.035*)**	0.310 **(0.030*)**	0.209 (0.151)	-0.220 (0.129)	0.030 (0.839)
ADHD- total score	-0.270 **(0.012*)**	0.396 **(<0,001*)**	0.254 **(0.019*)**	-0.176 (0.107)	-0.056 (0.612)
ODD	-0.307 **(0.030*)**	0.422 **(0.002*)**	0.357 **(0.011*)**	-0.204 (0.155)	-0.124 (0.393)
CD	-0.293 (0.309)	0.520 (0.056)	0.649 **(0.012*)**	-0.338 (0.237)	-0.416 (0.139)

AD: Attention-Deficit, HI: Hyperactivity-Impulsivity, ADHD: Attention-Deficit Hyperactivity Disorder, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder
SCA: Self-Confident Approach, SA: Submissive Approach, HSA: Helpless Styles Approach, OA: Optimistic Approach, SSSA: Seeking of Social Support Approach, r: Correlation Coefficient
*p<0.05
Spearman Correlation Analysis was used.

Considering the characteristics of the pandemic, there was not significant difference between ADHD, ODD and CD scores and the frequency with which the child met friends over the Internet during the pandemic, whether they followed online classes, and the change in sleep patterns and time.

13 (14.1%) of the participants had COVID-19 and there was no significant difference in terms of ADHD subtypes, gender, age and medication use compared to the group without COVID-19 infection. There was no significant difference between pre- and post-pandemic scores for AD, HI, total ADHD, ODD and CD in those with COVID-19 infection.

There was no significant difference between OA and SSSA coping mechanisms for stress and any subgroup (Table 3). A significant difference was observed between all subgroups except SA and CD and all subgroups except HSA and ADHD-HI ($p<0.05$).

DISCUSSION

Our study aimed to investigate the impact of the COVID-19 pandemic on the severity of ADHD, ODD and CD symptoms, to assess their interaction with socio-demographic data and to determine patients' coping mechanisms with stress. In a study by Lee (17), school routines were a supportive and important coping mechanism, especially for children and adolescents with mental health problems. During the pandemic the schools were closed and this protective mechanism disappeared. It has therefore been suggested that patients' symptoms may have increased. In another study, it was emphasized that as a result of the closure of schools due to COVID-19 restrictions, children and adolescents with ADHD may suddenly cease their relationships with classmates, which may lead to adaptation problems and this feeling of

loneliness may negatively affect mental health (17,18). However, our study found a significant decrease in the severity of ADHD, ODD and CD symptoms during the pandemic. One study suggested that the increase in well-being of children with ADHD during the quarantine period may be due to a reduction in school-related anxiety, parents' flexibility in adapting to their children's rhythms, and increased awareness of their children's daily difficulties.

Similar to our findings, this study found that attention problems were improved. This situation was associated with a more suitable home environment for learning. It is suggested that the absence of the excessive stimuli of the classroom environment in the home environment may have led to a reduction in inattention and impulsivity during the quarantine period, and that a flexible study program designed to take account of the child's fatigue status, the presence of both parents to help with homework, and personalized help for the child increased the child's success at school. It has been noted that as a result of the reduction in time constraints caused by school, longer, more consistent and better quality time may have been spent with family, which may have strengthened family relationships and led to a reduction in symptoms of ODD and CD (19). Similarly, in our patients, family relationships were strengthened during the pandemic, which may have led to a decrease in the symptoms of ODD and CD.

A study conducted by Dvorsky et al (20) found that, contrary to what was expected, young people with ADHD were less distressed by COVID-19 than their peers without ADHD. The fact that young people with ADHD experience emotion regulation disorder has been found to be related to co-diagnosis (21). It has been reported that while emotion regulation disorder may be a risk factor for psychopathology, well-developed emotion regulation capabilities may also serve as an essential buffer against chronic stress (22). The fact that most of the patients participating in our study are currently taking medication and continuing their regular follow-up appointments in the last year before the pandemic may have prevented ADHD symptoms from being adversely affected as a result of resolving their emotion regulation problems and reducing their anxiety levels. Despite the negative effects of the pandemic and increased risks, some factors, such as flexibility and increased time spent with family, less exposure to negative peer interactions at school, suggest that children and adolescents with ADHD may also experience positive effects in some areas during the COVID-19 pandemic (23). In particular, home-based education may remove some of the school-related stressors, such as frustration and social difficulties resulting from failure, that children and adolescents with ADHD often experience (24,25). In our study, the fact that clinical symptoms decreased in children and adolescents with ADHD suggests that patients may have experienced positive effects for similar reasons. In addition, the fact that 78.3% of our participants did not attend online classes and 43.5% spent time on the Internet in their spare time suggests that an uncontrolled environment may have developed at home and that children/adolescents may not have been forced to engage in boring activities such as listening to lectures and studying. In addition, the exclusion of patients with comorbidities such as major depressive disorder and anxiety disorder from the study and the continuation of the follow-up and treatment process in our clinic, albeit online, may have played a role in the reduction of symptoms. Although patients experienced some positive effects during this period, it is likely that continued school attendance is as important for children with ADHD as it is for other children. Contrary to the results of our study, many published studies have shown that the severity of ADHD symptoms increased during the COVID-19 pandemic (22,26). These studies show that pandemic-related disruptions in daily routines and stay away from life activities significantly exacerbate the impairment in functioning experienced by individuals with ADHD (27). Reduced exercise and time spent outdoors, less enjoyment of activities performed and increased screen time have been associated with the development of negative mood (28).

In their guidelines on the assessment and management of ADHD during the COVID-19 pandemic (27), the European ADHD Guideline Group stated that if individuals with ADHD are clinically diagnosed following an appropriate assessment, they should be started on treatment or continue taking medication if they are already on medication. Given that COVID-19 restrictions and physical distancing can increase the risks associated with ADHD, it is reported in the guideline that there is no need for a drug holiday during the current crisis period. In our patients, drug treatment was continued in a similar way, necessary dose adjustments were made by continuing drug treatments with online interviews during the most severe periods of the pandemic, patients' access to medication was facilitated, and drug holidays were not recommended to patients in accordance with the guidelines. As a result of our study, it was found that patients taking medication during the pandemic period showed significant improvement in ADHD, ODD and CD symptoms compared to the pre-pandemic period, and patients were in relatively good condition.

Understanding the factors that improve resilience, particularly in individuals with neurodevelopmental disorders, and thus prevent the negative psychological impact of COVID-19, is critical to facilitating individuals' adaptation to their current situation and reducing risk (20). Based on this perspective, our study investigated the coping mechanisms used by children and adolescents with ADHD to cope with stress. In a previous study, individuals with ADHD were found to use significantly more maladaptive and less flexible coping mechanisms than controls (29). As ADHD severity increases, the likelihood of using adaptive coping mechanisms for stress such as distraction, minimization, self-glorification by comparing with others, and seeking social support decreases, while the risk of using maladaptive coping mechanisms for stress, such as avoidance and social withdrawal increases (30). Dvorsky et al (20) found that adolescents with ADHD used adaptive coping behaviors less during the COVID-19 pandemic. In our study, it was found that ADHD-AD patients were significantly more likely to use negative coping mechanisms for stress, such as submissive and helpless approaches. This may be due to the fact that patients in this group were calmer, less intrusive and more introverted than those with ADHD-HI, ADHD-total, ODD or CD. Although it was observed that both positive and negative coping mechanisms were used together in patients with ADHD-HI, ADHD-total and ODD, it can be thought that the methods used contradict each other. This may be due to the age difference between the patients included in the study and the fact that the young age group's ability to cope with stress had not yet developed. The fact that patients co-diagnosed with CD were significantly more likely to use the helplessness approach suggests that they were blaming themselves for the problems they were experiencing and looking for outside help rather than seeking a solution. In addition, our study found that the least used methods by patients were the optimistic approach and seeking social support. The lack of an optimistic approach shows that the patients exaggerated when trying to solve the problems and they were angry about the events, they looked at the events from a negative angle and they did not treat themselves tolerantly. The absence of seeking social support means that they did not share their problems with others. Failure to use these methods may be due to previous negative experiences of patients such as being labelled in social settings, difficulty in making friends, not finding the support they expected when seeking social support, and fear of negative feedback/criticism.

A study of children and adolescents diagnosed with ADHD in France during the quarantine period assessed the impact of the COVID-19 pandemic on the psychological well-being of children and adolescents. This study reported that children and adolescents had fewer difficulties due to school closures during the quarantine period, their anxiety about school was reduced, and there was no deterioration in their general well-being (19). In addition, the fact that ADHD symptoms were more likely to be observed in the classroom environment and that

less negative feedback was received from teachers and friends as a result of school closures may have supported this situation. According to our results, in particular, ADHD symptoms decreased significantly during the pandemic period in both the child (7-11 years) and adolescent (12-18 years) age groups, and there was no significant difference in coping mechanisms. This situation also suggests that patients with ADHD in both age groups have adapted well to the pandemic period.

Limitations of our study include the cross-sectional nature of the study, the lack of a control group, diagnoses not made by semi-structured interviews such as the K-SADS-PL, scores based on parental report only, and ADHD symptoms not measured by neuropsychological tests.

CONCLUSION

In conclusion, children and adolescents with ADHD are particularly at risk when adapting to chronic stressful situations such as the COVID-19 pandemic. Therefore, the importance of teaching adaptive coping strategies and establishing consistent daily routines is emphasized to increase resilience in these individuals (20). The researchers' literature review did not find a similar study conducted during the pandemic. Therefore, it is expected that the results of our study will contribute to the literature. In addition, it is predicted that our study may be essential to draw attention to the assessment of coping mechanisms and the development of healthy practices among ADHD patients and their parents who sought assistance from child and adolescent mental health outpatient clinics.

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The Patient Safety Culture Scale in Patient Falls: A Scale Development Study

Hasta Düşmelerinde Hasta Güvenliği Kültürü Ölçeği: Bir Ölçek Geliştirme Çalışması

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Abstract

Introduction: Patient safety culture is a very important concept for both patients and employees. It is more important for nurses, who make up the majority among health professions and spend more time with patients during working hours. Although there are many studies within the scope of patient safety in the literature, there is no scale study specific to patient falls for nurses.
Objective: In this study, it was aimed to develop the "Patient Safety Culture Scale in Patient Falls", which is thought to have an important place within the scope of patient safety culture and is not included in the literature specifically for patient falls.
Method: This study is a scale development study, which was designed according to the stages recommended for scale development studies in the literature. The draft scale (45 items) created by the researchers was primarily presented to the expert opinion. 15 items were eliminated in line with expert opinions and a draft scale of 30 items was obtained. Explanatory and confirmatory factor analyses, test-retest method and internal consistency analysis were used as statistical methods. A measurement structure consisting of 4 sub-dimensions and 23 items was obtained as a result of the exploratory factor analysis. The validity of this construct was confirmed by confirmatory factor analysis. The reliability of the scale was examined by test-retest reliabilty and internal consistency analysis.
Results: The stability coefficient of the scale was determined as 0.929 and the Cronbach Alpha internal consistency coefficient as 0.891 after the analysis
Conclusion: The findings obtained from the study show that "The Patient Safety Culture Scale in Patient Falls" is a valid and reliable measurement tool for the nurses in the sample. It is thought that "The Patient Safety Culture Scale in Patient Falls", will contribute to the preventive studies by evaluating the awareness level of the nurses working in the field.

Keywords: Patient Safety Culture, Patient Falls, Scale Study, Nursing Care Practices.

Özet

Giriş: Hasta güvenliği kültürü hem hasta hemde çalışanlar açısından oldukça önemli bir kavramdır. Sağlık meslek grupları arasında büyük bir çoğunluğu oluşturan ve çalışma saatleri içerisinde hastalara daha fazla vakit ayıran hemşireler için ise daha fazla önem taşımaktadır. Literatürde hasta güvenliği kapsamında birçok çalışma olmasına rağmen hemşirelere yönelik hasta düşmeleri özelinde yapılmış bir ölçek çalışması bulunmamaktadır.
Amaç: Bu çalışmada hasta güvenliği kültürü kapsamında önemli bir yere sahip olduğu düşünülen ve hasta düşmelerine özel literatürde yer almayan "Hasta Düşmelerinde Hasta Güvenliği Kültürü Ölçeği"nin geliştirilmesi amaçlandı.
Yöntem: Çalışma, literatürde ölçek geliştirme çalışmaları için önerilen aşamalara göre tasarlanmış bir ölçek geliştirme çalışmasıdır. Araştırmacılar tarafından oluşturulan taslak ölçek (45 madde) öncelikle uzman görüşüne

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sunuldu. Uzman görüşleri doğrultusunda 15 madde elenmiş ve 30 maddelik taslak ölçek elde edildi. İstatistiksel yöntemler olarak açıklayıcı ve doğrulayıcı faktör analizleri, test-tekrar test yöntemi ve iç tutarlılık analizi kullanıldı. Açımlayıcı faktör analizi sonucunda 4 alt boyut ve 23 maddeden oluşan bir ölçüm yapısı elde edildi. Bu yapının geçerliliği doğrulayıcı faktör analizi ile doğrulandı. Ölçeğin güvenirliği test-tekrar test güvenirliği ve iç tutarlılık analizi ile incelendi.

Bulgular: Analiz sonucunda ölçeğin kararlılık katsayısı 0,929 ve Cronbach Alpha iç tutarlılık katsayısı 0,891 olarak belirlendi.

Sonuç: Çalışmadan elde edilen bulgular, "Hasta Düşmelerinde Hasta Güvenliği Kültürü Ölçeği"nin örneklemdeki hemşireler için geçerli ve güvenilir bir ölçme aracı olduğunu göstermektedir. "Hasta Düşmelerinde Hasta Güvenliği Kültürü Ölçeği"nin sahada çalışan hemşirelerin farkındalık düzeylerini değerlendirerek önleyici çalışmalara katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: Hasta Güvenliği Kültürü, Hasta Düşmeleri, Ölçek Çalışması, Hemşirelik Bakım Uygulamaları.

INTRODUCTION

Patient falls are undesirable situations that develop in all institutions where health care is provided. Patient falls develop due to both patient-related factors and the inadequacy of the measures taken by institutions within the scope of patient safety. Regardless of the reason, patient falls occur as an important problem that threatens patient safety in all institutions providing health care services. Patient falls, which cause the onset of a difficult and troublesome process from the patient's point of view, are an important and preventable patient safety problem (1-5).

Patient falls take the first place among the situations that threaten patient safety worldwide. Regardless of other health problems, both individuals and their families are greatly affected in terms of quality of life due to complications that develop due to falling; because falls can cause many complications, such as injuries, disabilities, the development of fractures at different levels, an increase in the need for additional treatment, an increase in the length of hospitalization, and death (4,6).Looking at the literature, studies in which patients are given the risk of falls and rates of fall development during the provision of services in medical institutions show that the results are distributed over a wide range. The main reason for this situation is the change in the characteristics of the patient population and clinic. Differences in the definition of falls, keeping records in order, differences in prevention strategies and evaluation methods are also other important factors affecting the results (7,8).

The view and awareness of healthcare professionals about patient safety culture has significant effects on patient falls. Ensuring patient safety during nursing care and practices always has an important place. Nursing is a profession that will greatly contribute to reducing falls if they plan proper care by determining the patient's risk status (7,9).

METHOD

Our study is a scale development study, and it was planned by considering the literature review and all the methodological steps that should be done in a scale development study (10). These stages and their sub-headings are given in Figure 1.

Stage 1: Creating the Draft Scale
- Literature review.
- Creating the item pool.

↓

Stage 2: Ensuring the Content Validity of the Draft Scale
- Submitting the items in the item pool to the opinion of nurse academicians who are experts

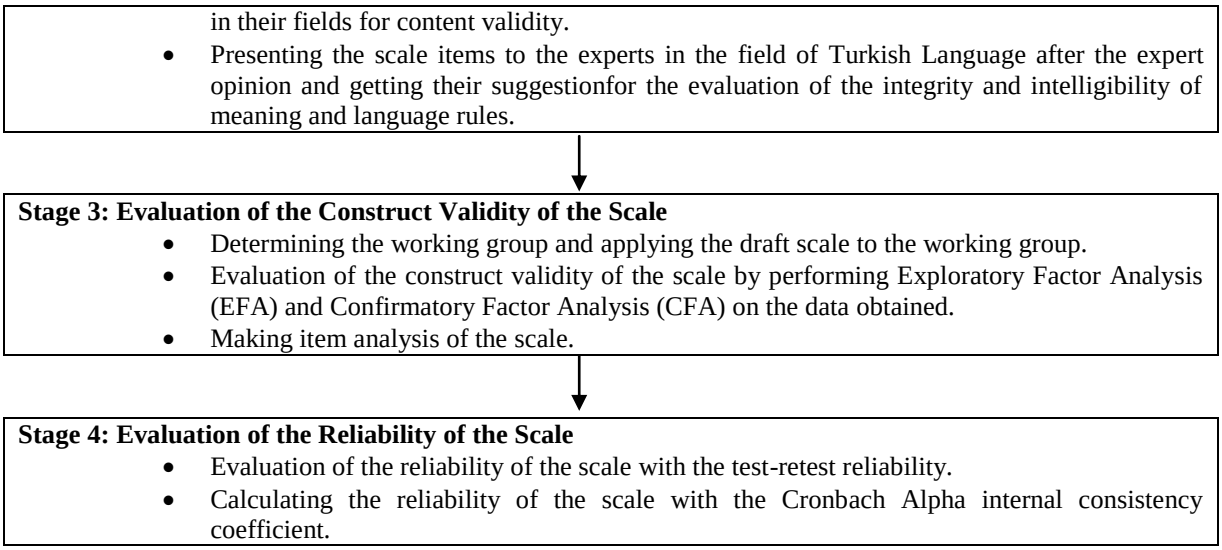

Figure 1. Process of the "Patient Safety Culture Scale in Patient Falls" development

The Structure of the Scale

The "Patient Safety Culture Scale in Patient Falls" that we plan to develop is planned as a 7-point Likert type scale. The items in the scale range from 1 point to 7 points, and the scoring is as follows: "7=strongly agree", "6=agree", "5=somewhat agree", "4=neither agree nor disagree", "3=somewhat disagree", "2=disagree" and "1=strongly disagree". The closer to 7 points, the higher the level of agreement with the statement in the relevant item, and the closer to 1 point, the lower the level of agreement to the statement in the relevant item.

Process of the "Patient Safety Culture Scale in Patient Falls" Development

Stage 1: Creating the Draft Scale

Literature review: The items in the item pool of the draft scale were created by scanning the literature. In this context, a scan was made using the concepts of patient falls, nursing care, and patient safety. Source books and guides for nursing practices have also been examined for this purpose (11-15).

Creating the item pool: After a literature review, the item pool of the draft scale was created by the researchers. There were a total of 45 items in the draft scale created, 43 of which were positive and 2 of which were negative.

Stage 2: Ensuring the Content Validity of the Draft Scale

Submitting the items in the item pool to the opinion of nurse academicians who are experts in their fields for content validity: Content validity defines the adequacy of the items in the scale that is planned to be developed for the power to cover the situation intended to be measured. According to this definition, the items included in the scale should have the property of measuring, and the full detail of the quantity planned to be measured should be questioned by the items on the scale. In other words, the developed measurement tool has content validity at the level that it measures the conceptual infrastructure of the quantity intended to be measured in all aspects (10). The items of the first draft scale were submitted to the opinion of 11 academicians who are experts in the field of nursing in order to evaluate them in terms of content validity. The experts whose opinions were obtained have doctoral degrees in different fields of nursing and are working as academicians. The draft scale was sent to the e-mails of the experts and evaluations were made, and the evaluations returned by e-mail were accepted.

A Content Validity Index (CVI) analysis was performed for the items that were notified that they should not be in the item pool according to the experts' opinions. Depending on the results of the analysis, 15 items were removed from the scale and a new draft scale consisting of 30 items was obtained.

*Presenting the scale items to the experts in the field of Turkish Language and getting their suggestionfor the evaluation of the integrity and intelligibility of meaning and language rules:*The opinions of two academicians specializing in the field of Turkish Language were taken in order to evaluate the conformity and intelligibility of the new draft scale to the spelling rules of the articles. The statements were rearranged according to the suggestions presented and the final version of the draft scale was developed.

Stage 3: Evaluation of the Construct Validity of the Scale

Determining the working group and applying the draft scale to the working group: The study group of the research consisted of 550 nurses working in a Education and Research Hospital in Turkey. Simple random sampling method was used to determine the study group. The nurses included in the sample were informed about the purpose of the study and the nurses who agreed to participate in the study on a voluntary basis and filled out the scale items were allowed to participate in the study. The study data were collected by online surveys. The questionnaires were sent to the nurses online and the nurses were asked to fill in the questionnaires. At this stage, the questionnaires that were determined to be filled carelessly were not included in the evaluation. The data of 316 nurses for Exploratory Factor Analysis (EFA) and 255 nurses for CFA were included in the final evaluation. The data of 50 nurses were evaluated and the reliability of the scale was evaluated in the test-retest reliabilty, which was performed in the last stage. Data of 210 nurses were used for item analysis and calculation of Cronbach Alpha coefficient.

Ethical Dimension of the Study

For this study ethics committee approval was obtained from Adıyaman University Social and Human Sciences Ethics Committee. (Date: 29.07.2021, Issue: 124) and institution permission was obtained from the Ministry of Health Scientific Research Platform (Date: 25.06.2021, Form No: 2021-06-24_T12_27_01) Each participant was informed about the study and the questionnaires were sent online to the participants who agreed to participate in the study.

RESULTS

Stage 3: Evaluation of the Construct Validity of the Scale

Findings on Construct Validity

Factor analysis is a frequently used method in order to determine the measurement structure of the relevant scale in scale development studies. The general factor of the scale planned for development, information on the number of sub-dimensions and sub-dimensions are obtained by factor analysis. The basic structure of the scale is created by naming the sub-dimensions obtained after the analysis. It was aimed to determine the measurement structure of the scale with the data of 316 nurses and exploratory factor analysis (EFA) was performed on the data obtained at this stage of our study. The most important criterion is that the sample size is sufficient for the application of EFA. Kaiser-Meyer-Olkin (KMO) test statistics were used to determine the adequacy of the sample size. In the literature, a KMO value of 0.90 is accepted as perfect. If the KMO value is around 0.80, it is defined as very good. A KMO value between 0.70 and 0.60 is defined as fair, while below 0.50 is reported to be unacceptable (16).

According to the draft scale developed in our study, the KMO statistic was calculated as 0.874 in the data. This value shows that the sample size is very good and sufficient for our study (Table 1).

Another important test for the implementation of EFA is the Bartlett sphericity test. The Bartlett sphericity test is used to decode whether there are significant relationships between variables. The high correlation relationship between the variables is important for factor analysis (17). The Bartlett test statistic is expected to be high and significant in order to ensure the assumption of sphericity (16). It was determined in the draft scale that we developed in our study that there is both a high and significant relationship between the variables and the assumption of sphericity is provided ($\chi 2$=6155,481; p<0,001).

EFA was applied to 30 items in the scale by basic components analysis and varimax rotation methods. to determine the factor structure of the scale we plan to develop. After this analysis, 7 overlapping items that did not fit into any factor were removed from the draft scale. EFA was reapplied to the remaining 23 items (Table 1).

Table 1. Results of EFA

Sub dimensions	Items	Factor Load Value	Eigenvalue	Variance (%)	Cumulative Variance (%)
Factor 1	Item 1	0.693	10.589	35.298	35.298
	Item 2	0.843			
	Item 4	0.852			
	Item 5	0.751			
	Item 6	0.844			
	Item 7	0.601			
	Item 10	0.836			
	Item 11	0.728			
	Item 12	0.841			
Factor 2	Item 18	0.708	3.072	10.240	45.538
	Item 19	0.537			
	Item 20	0.668			
	Item 21	0.716			
	Item 23	0.672			
Factor 3	Item 27	0.715	1.838	6.128	51.666
	Item 28	0.807			
	Item 29	0.702			
	Item 30	0.774			
Factor 4	Item 13	0.752	1.606	5.354	57.020
	Item 14	0.587			
	Item 16	0.565			
	Item 17	0.782			
	Item 26	0.635			

The coefficient of self-worth is an important value used to determine the number of factors, and the fact that it is equal to 1 or greater than 1 indicates the appropriateness of the factors. In the literature, this criterion is known as the Kaiser criterion (10). According to the EFA result, 4 sub-dimensions with an eigenvalue greater than 1 were obtained in our study. An important criterion both in determining the number of sub-dimensions and in ensuring the validity of the structure is the total described variance. According to the results of the EFA conducted in our study, the total variance of the 4-factor draft scale structure was found to be 57.020%. The variance rates explained by each factor were found to be 35.298% for Factor 1, 45.538% for Factor 2, 51.666% for Factor 3 and 57.020 for Factor 4 (Table 1).

It is reported in the literature that the factor load values of 0.45 and above are a sufficient criterion for item selection (18). In our study, it was determined that the factor loads of the

items were in the range of 0.537-0.852. In line with this finding, it can be stated that the factor loading levels of the items in the 4-factor model are high and sufficient.

CFA was performed using the AMOS 23 program to examine the validity of the measurement construct. Data from an independent sample of 210 nurses were used for CFA. Fit indices such as χ2/sd, GFI, CFI, TLI, IFI, RMSEA are used to evaluate whether the measurement model prepared after CFA practice is compatible with the data in the literature (19). The reference intervals of the relevant fit indices are classified in Table 2 as good fit and acceptable fit(20) and the values we obtained in our study are seen together in the same table.

Table 2. References and Scale Values of the Fit Indices

Fit Indices	Good Fit	Acceptable Fit	Scale Values
χ2/sd	≤ 3	≤ 5	2.767
GFI	≥ 0,90	≥ 0,85	0.897
IFI	≥ 0,95	≥ 0,90	0.936
TLI	≥ 0,95	≥ 0,90	0.913
CFI	≥ 0,97	≥ 0,95	0.973
RMSEA	≤ 0,05	≤ 0,08	0.683

GFI; goodness of fit index; IFI; incremental fit index; TLI; tucker-lewis index; CFI; comparative fit index; RMSEA; root mean square error of approxi-mation.

When the fit indices of the scale were examined, it was accepted that χ2/sd and CFI values showed good fit. For the IFI, TLI, GFI and RMSEA values, it was determined that these values showed an acceptable fit, and the validity of the 4 sub-dimensional measurementstructure was verified on an independent sample. The regression coefficient refers to the factor load of the items and it should be significant in the CFA (19). The standard factor load value above 0.40 in CFA is important for construct validity (21). The regression coefficients obtained with CFA are shown in Table 3.

Table 3. Standard Regression Coefficients of Items as a Result of CFA

Items	Factor 1	Factor 2	Factor 3	Factor 4
1. It is important to evaluate the risk of falling patients regularly with objective assessment tools.	0.731			
2. I attach importance to taking the necessary measures to prevent patients from falling.	0.726			
4. I know the importance of protective-preventive practices for the prevention of falls.	0.873			
5. I know the risky areas for patient falls in the hospital environment.	0.766			
6. I am aware of the factors that increase the risk of falls in patients.	0.728			
7. I provide training for all patients and their relatives to prevent falls.	0.629			
10. I take care that the borders of the patient beds are removed.	0.711			
11. I take care that the brakes of the patient beds are locked.	0.776			
12. I plan the practices to prevent falls during the transfer of patients from bed to stretcher and from stretcher to bed.	0.720			
18. The consequences of falls negatively affect the lives of patients and their relatives.		0.708		
19. Patient falls increase the cost of care.		0.737		
20. Providing education to patients and relatives is effective in preventing falls.		0.868		
21. I am aware that employee attitudes are important in preventing patient falls.		0.716		
23. Whether there is a risk of falling or not, a call ring device should be available to every patient.		0.772		
27. I report equipment malfunctions and deficiencies that may cause patients to fall.			0.715	
28. I ensure regular control of medical devices that may cause patients to fall.			0.807	
29. I take care not to keep unnecessary items in the patient's room that may cause tripping and falling in order to prevent patients from			0.702	

falling.				
30. When the transfer of patients to another department is planned, I convey the information about the risk of falling of the patient to the responsible nurse of the other department.			0.774	
13. I attend in-service trainings aimed at preventing patient falls.				0.752
14. It is the nurse's responsibility to assess the risk of patients falling.				0.787
16. I make sure that patients are not left alone in places with wet floors, such as bathrooms and toilets, in case they fall.				0.765
17. I ensure that my teammates participate in in-service trainings aimed at preventing patients from falling.				0.822
26. I know the right time when patients' fall risk should be re-evaluated.				0.635
AVE	0.552	0.581	0.563	0.569

CFA: Confirmatory Factor Analysis; AVE: Average Variance Extracted.

It is seen in Table 3 that the factor loads are greater than 0.40. This indicates that the developed scale is at an acceptable level in terms of construct validity. Another important indicator in terms of construct validity is AVE values. The AVE value provides information about whether the Items collected under the factor are in harmony. If this value is greater than 0.5, the factor has a compliance validity. If this value is less than 0.5, it refers to the measurement error, which means there is no compliance validity (22). It was found that the AVE value was greater than 0.5 in all factors (Table 3) in our study. In accordance with these findings, it can be stated that it has structural validity for the scale we are developing.

Findings Regarding Item Analysis

It was determined that the scale had Construct validity and item analysis was made with the data collected from 210 nurses. For this purpose, item analysis based on item total score correlation and item analysis based on lower and upper groups were made.

Item Analysis Based on Item-Total Point Correlation

Using the item analysis evaluation based on the item-total score correlation, it is evaluated whether there is a correlation between the scores of each item in a scale and the total score obtained from the scale. Then a decision is taken on which items should be removed from the scale (23). Items with a coefficient value lower than 0.20 are removed from the scale, while items higher than 0.30 remain on the scale because they are similar to the overall scale. Items with a coefficient of 0.20-0.30 are evaluated according to their status on the scale and it is decided whether they will remain or not (18).

As a result of the analysis, it was determined that the item total correlation coefficient was greater than 0.30 in all 23 items. It was determined that the relevant items moved in the same direction as the entire scale, and at this stage, no items were removed from the scale (Table 4).

Table 4. Total Point Correlation of Items

Item	Total Point Correlation of Items	Item	Total Point Correlation of Items
Item 1	0.566	Item 17	0.522
Item 2	0.612	Item 18	0.491
Item 4	0.487	Item 19	0.422
Item 5	0.459	Item 20	0.518
Item 6	0.542	Item 21	0.631
Item 7	0.623	Item 23	0.643
Item 10	0.391	Item 26	0.388
Item 11	0.511	Item 27	0.586
Item 12	0.532	Item 28	0.513
Item 13	0.518	Item 29	0.453
Item 14	0.583	Item 30	0.571
Item 16	0.601		

Item Analysis Based on Lower and Upper Groups

It is recommended to conduct item analysis based on the lower and upper groups in order to select items that have the ability to distinguish between likert-type scale development studies in the literature (24). In order to examine the distinguishing capacities of the 23 items included in the scale in this diagram, the total scores of the scale obtained with the participation of 210 nurses were sorted from largest to smallest. The total score averages of the participants were t-tested for independent samples for the data of 57 nurses in the lower and upper groups of 27% (Table 5). In addition, a comparison was made for the entire scale and for each item separately (Table 6). It was found that the difference was statistically significant when the mean scores of the lower and upper groups were compared ($p<0.05$). When the average scores between the upper and lower groups of the 23 items in the scale were compared, it was determined that there was a significant difference ($p<0.05$). The findings show that all 23 items in the scale are distinctive and should remain in the scale.

Table 5. Comparison of the Lower and Upper Group Averages of the Scale

Groups	N	x̄	SD	t	p
Upper	57	71.63	8.45	19.558	0.001
Lower	57	145.36	2.34		

*p<0.01

Table 6. Comparison of the Means for Item Discrimination

Item	Group	N	x̄	SS	t	p	Item	Group	N	x̄	SS	t	p
Item 1	Upper	57	6.75	0.71	11.521	0.000	**Item 13**	Upper	57	6.43	1.42	4.573	0.001
	Lower	57	3.23	0.58				Lower	57	3.24	1.53		
Item 2	Upper	57	6.62	1.02	9.610	0.000	**Item 14**	Upper	57	6.17	1.27	22.17	0.000
	Lower	57	2.96	0.78				Lower	57	2.03	1.45		
Item 3	Upper	57	6.18	0.55	7.662	0.001	**Item 15**	Upper	57	6.73	0.21	3.881	0.000
	Lower	57	3.01	0.82				Lower	57	3.12	1.11		
Item 4	Upper	57	5.97	1.12	10.592	0.000	**Item 16**	Upper	57	5.59	1.03	7.412	0.000
	Lower	57	3.08	0.85				Lower	57	2.08	0.42		
Item 5	Upper	57	6.45	0.73	13.411	0.000	**Item 17**	Upper	57	6.78	0.84	5.457	0.000
	Lower	57	2.93	0.47				Lower	57	3.13	1.13		
Item 6	Upper	57	5.88	0.51	10.084	0.000	**Item 18**	Upper	57	5.84	0.43	6.236	0.000
	Lower	57	3.08	0.63				Lower	57	3.78	1.16		
Item 7	Upper	57	6.06	0.29	12.281	0.000	**Item 19**	Upper	57	6.41	0.12	14.213	0.001
	Lower	57	4.23	0.89				Lower	57	3.17	0.41		
Item 8	Upper	57	5.78	0.84	8.082	0.000	**Item 20**	Upper	57	6.78	1.22	3.775	0.000
	Lower	57	3.27	1.12				Lower	57	2.84	0.41		
Item 9	Upper	57	4.89	0.75	6.123	0.001	**Item 21**	Upper	57	5.87	0.49	5.121	0.000
	Lower	57	2.45	0.53				Lower	57	3.41	0.75		
Item10	Upper	57	5.51	1.42	15.174	0.000	**Item 22**	Upper	57	6.11	1.14	6.421	0.000
	Lower	57	3.07	0.43				Lower	57	2.81	0.91		
Item 11	Upper	57	4.24	1.53	13.112	0.000	**Item 23**	Upper	57	5.78	2.01	4.374	0.001
	Lower	57	2.86	2.12				Lower	57	2.64	1.22		
Item 12	Upper	57	6.81	0.72	11.964	0.000							
	Lower	57	2.87	1.84									

*p<0.01

Stage 4: Evaluation of the reliability of the scale

Findings Regarding the Reliability of the Scale

Test-Retest Reliability of the Scale: It is recommended to apply the draft scale at least twice with an interval of fifteen days for test-retest reliabilty in scale development studies. The fact that the scores obtained from the scale are similar between the results of these two

applications indicates the similarity of the two results.Stability is a well-known reliability criterion in measurement tools that include measuring characteristics whose continuity is like attitudes, the ability to change is limited, and which are not easily changed in their target (16).

The stability of the scale we developed in our study was evaluated using the test-retest reliabilty on data collected from 50 nurses. The scale was applied with an interval of 20 days and the difference between the first and second application scores of the total and sub-dimensions was evaluated with the dependent group's t-test. Afterwards, the Pearson correlation coefficients between the two applications were calculated. The stability coefficients of the total and sub-dimensions of the scale are shown in Table 7.

Table 7. Test-re-Test Application Results

	Application	N	$\bar{x}$	SS	t	p	r	p
Interest	1.	50	47.21	3.85	0.769	0.352	0.923	0.000
	2.	50	47.83	4.09				
Information	1.	50	26.84	13.25	0.531	0.285	0.926	0.000
	2.	50	26.55	13.41				
Attention	1.	50	18.73	7.85	0.402	0.212	0.952	0.000
	2.	50	18.57	7.51				
Awareness	1.	50	29.52	14.37	0.543	0.292	0.937	0.000
	2.	50	29.39	14.75				
Total	1.	50	142.86	8.96	1.385	0.523	0.929	0.000
	2.	50	143.12	8.63				

*p<0.01

Considering the total and sub-dimensions of the scale, no significant difference was found between the results of the 1st and 2nd application (p>0.05). Finding similar results after the applications shows the reliability of the scale. However, it was determined that the test retest stability coefficients of the total and sub-dimensions of the scale were quite high and significant (p<0.01).

Internal Consistency Analysis

In Likert type scale development studies, there should be a relationship between the feature that is aimed to be measured and the items in the scale. Each item on the scale should measure similar attitude (16). The Cronbach α coefficient is used to check this hypothesis and to determine the reliability level. If the Cronbach α coefficient is greater than 0.70, the scale is considered reliable (10) and it is also stated that the higher this coefficient, the more consistent the items in the scale are (23).

The data of 210 nurses and the total scale and Cronbach's α coefficients for each sub-dimension were calculated in the item analysis phase of the internal consistency reliability of the scale we developed within the scope of our study. The relevant values are shown in Table 8 and each Cronbach α coefficient is greater than 0.70.

Table 8. Cronbach α coefficients of the total and sub-dimensions of the scale

	Number of Items	Cronbach α
Interest	9	0.851
Information	5	0.812
Attention	4	0.826
Awareness	5	0.752
Total	23	0.891

DISCUSSION

Our study aims to develop a scale that will measure nurses' awareness of their own practices regarding patient safety culture for patient falls, and to establish the validity and reliability of

this scale. In this context, the 45 item item pool created by the researchers was primarily evaluated with expert opinions and necessary analyzes. 15 of these substances were eliminated. Then, the draft scale consisting of 30 items was finalized by taking expert opinion in terms of language and meaning.

EFA was applied to determine the factor structure of the developed draft scale, and the items that could not be placed on any factor and were overlapping were removed from the scale. The scale structure consisting of 4 sub-dimensions and 23 items was obtained at this stage and it was determined that this scale explained 57.020% of the total variance. It has been reported that the limits of total variance should be between 40% and 60% in the literature (19).

It is reported in the literature that it is sufficient to have factor loads of Items obtained as a result of EFA above 0.45 (18). The factor loads of the scale that we developed changed between 0.537-0.852 within the scope of our study. In this direction, it can be stated that the factor load values are high and sufficient. The CFA was performed with an independent sample after this procedure. As a result of the CFA, it was determined that the scale model consisting of 4 sub-dimensions and 23 Items was compatible and the scale structure created with the EFA was valid on another sample. Factor loadings of all items were found to be high and significant after CFA. In addition, it was observed that the AVE values of the factors were higher than 0.50. These findings show that the scale has construct validity (10).

Item analysis was performed within the scope of Item-total correlation to Items belonging to “The Patient Safety Culture Scale in Patient Falls". It is requested in the literature that the correlation coefficient be greater than 0.30. It was found that the correlation coefficients of all the items in our study were higher than the lower limit (18). It has been determined that the whole scale and all of the Items have distinctive features as a result of the item analysis based on the lower and upper groups, which is a different item analysis.

The stability of the scale was determined by applying the scale developed in our study to the same sample twice in twenty days. It was determined at this stage that the scores for both the total scale and its sub-dimensions were similar and the stability coefficients were greater than 0.70. It can be stated that the measurement results of the scale developed in line with these findings are invariant, stable and reliable. The Cronbach α coefficients of the whole scale and its sub-dimensions were calculated to evaluate the internal consistency of the scale. Cronbach's α coefficients were found to be greater than 0.70 in the entire scale and its sub-dimensions.

The absence of a scale specific to patient falls in the literature, which is an important issue within the scope of patient safety, is the starting point of our research. The fact that it is aimed at an original area within patient safety increases the originality of the research. It is thought that the scale, which is planned to be developed, will contribute to the preventive studies by evaluating the awareness level of the nurses working in the field.

When the literature is examined, it has been seen that studies on falls are mostly studies on determining the risk of falling in patients, factors related to falling risk and preventing falls such as training methods, programs and tools, hospital systems development, policy and procedure development (7,25,26). Scale studies on patient safety are also included in this context. However, the section on falls covers a certain part of the scale. In other words, there are scales focused on patient safety as a broad concept (27,28). The scales related to patient falls are planned as fall risk determination scales. The scale we have developed in our study differs due to the way it is planned to contribute to the measurement of a specific area within the concept of patient safety from the point of view of nurses.

Another important point in the prevention of falls is related to the importance and value given to this issue. As the first and most important stage of prevention of patient falls, both individual and institutional culture should be formed. Establishing a safety culture is the first step of starting research and development studies, planning of other applications and developing an attitude for prevent the patient falls. Therefore, in this study, it is aimed to develop a scale that enables the definition of culture.

CONCLUSION

In accordance with the data and findings obtained from the study, it can be stated that "The Patient Safety Culture Scale in Patient Falls", is a valid and reliable measurement tool for patient falls on the relevant sample. The final version of the scale consists of 4 sub-dimensions and 23 items. All of the items in the scale are positive. Cronbach's alpha values for the sub-dimensions (Interest, Knowledge, Attention, Awareness) were determined as 0.851, 0.812, 0.826, 0.752, and 0.891 for the total scale, respectively.
It is thought that this scale will contribute to the preventive studies by evaluating the awareness level of the nurses working in the field. It is recommended to use this scale in other studies to be designed in the future, to demonstrate validity and reliability on the sample in related studies, to define individual and institutional culture for the prevention of falls, and to plan remedial development activities.

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Sleep Quality and Factors Affecting The Sleep Quality of Patients Presenting to Traditional and Complementary Medicine Centre

Geleneksel ve Tamamlayıcı Tıp Merkezine Başvuran Hastaların Uyku Kaliteleri ve Uyku Kalitelerini Etkileyen Faktörler

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Abstract

Introduction: No studies were encountered in the literature on the effects of traditional and complementary treatments on sleeping problems experienced by patients who underwent those procedures due to other health problems.
Objective: This study aims to determine sleep quality and the factors that affect it among patients presenting to traditional and complementary medicine centre due to various health problems.
Method: A total of 314 patients presenting to traditional and complementary medicine centres were included in this cross-sectional study. Data were obtained with a personal information form, the Cumhuriyet Subjective Sleep Quality Scale, and the Sleep Hygiene Index. The study was reported according to STROBE guidelines.
Results: The median Cumhuriyet Subjective Sleep Quality Scale score of the patients was 22 (IQR: 19) and the median Sleep Hygiene Index score was 25.00 (8.00). It was determined that gender, income, and daily sleep duration had statistically significant effects on sleep quality ($p<0.05$). It was reported by 42.6% of the patients who underwent acupuncture treatment, 37.5% of the hypnosis treatment patients, 40.3% of the cupping treatment patients, 52.4% of the ozone therapy patients, 42.9% of the mesotherapy patients, and 47.5% of the hirudotherapy patients that, compared to before, they had much better sleep after undergoing these treatments.
Conclusion: It was determined in this study that the sleep quality and sleep hygiene of the patients were good. Traditional and complementary therapies can be considered to improve patients' sleep quality and hygiene.

Keywords: Traditional and Complementary Medicine, Sleep Quality, Sleep Hygiene.

Özet

Giriş: Literatürde diğer sağlık sorunları nedeniyle geleneksel ve tamamlayıcı tedavi alan hastalarda, geleneksel ve tamamlayıcı tedavinin uyku sorunlarına etkisini inceleyen çalışmalara rastlanılamamıştır.
Amaç: Bu çalışmanın amacı, çeşitli sağlık sorunları nedeniyle geleneksel ve tamamlayıcı tıp merkezine başvuran hastaların uyku kalitesi ve uyku kalitesini etkileyen faktörleri belirlemektir.

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Yöntem: Bu kesitsel çalışmaya geleneksel ve tamamlayıcı tıp merkezine başvuran toplam 314 hasta dahil edildi. Veriler Kişisel Bilgi Formu, Cumhuriyet Öznel Uyku Kalitesi Ölçeği ve Uyku Hijyeni İndeksi ile toplandı. Çalışma STROBE yönergelerine göre rapor edildi.
Bulgular: Hastaların Cumhuriyet Öznel Uyku Kalitesi Ölçeği ortanca puanının 22 (IQR: 19) ve Uyku Hijyeni İndeksi ortanca puanın ise 25,00 (8,00) olduğu belirlendi. Cinsiyet, gelir düzeyi ve günlük uyku süresinin uyku kalitesini istatistiksel olarak anlamlı düzeyde etkilediği saptandı ($p<0,05$). Bu çalışmada akupunktur tedavisi alan hastaların %42.6'sının, hipnoz tedavisi alan hastaların %37.5'inin, hacamat tedavisi alanların %40.3'ünün, ozon tedavisi alanların %52.4'ünün, mezoterapi hastalarının %42.9'unun ve hirudoterapi hastalarının %47.5'inin önceki zamana kıyasla daha iyi uyudukları belirlendi.
Sonuç: Bu çalışmada, hastaların uyku kalitesi ve hijyenlerinin iyi olduğu görülmüştür. Geleneksel ve tamamlayıcı tedavilerin hastaların uyku kalitesi ve hijyenini geliştirdiği düşünülebilir.

Anahtar Kelimeler: Geleneksel ve Tamamlayıcı Tedavi, Uyku Kalitesi, Uyku hijyeni.

INTRODUCTION

As well as being a crucial component of health, sleep, as a physiological process, is a physiological necessity just like air, water, and food. The fundamental function of sleep is to enable the body to restore energy and rest. Sleeping plays a significant role in physical performance, memory, and learning. Sleep is also necessary for metabolic events and emotional regulation (1).

Sleep quality is defined as the individual's satisfaction with the sleeping experience. Sleep quality has four attributes: sleep efficiency, sleep latency, sleep duration, and wake after sleep onset (2). Countless practices can increase sleep quality by improving these factors in a positive direction. These practices, which are also called sleep hygiene, include the regulation of environmental factors that contribute to comfortable and quality sleep and the modification of personal habits. Sleep hygiene is said to play a substantial role in improving sleep quality (1).

Sleep quality affects individuals' health (2). Decreased sleep quality can cause dysfunction, anger, fatigue, slowed reactions, and increased caffeine or alcohol consumption in individuals. Low sleep quality can also result in health problems such as diabetes, obesity, heart disease, injuries, psychological problems, anxiety, and depression (2,3). Therefore, improved sleep quality is necessary to avoid such adverse outcomes. As well as ensuring sleep hygiene, various interventions, such as implementing traditional and complementary medicine practices, are used to improve sleep quality. It has been revealed in the literature that traditional and complementary treatments improve sleep quality (4,5). It was indicated in a systematic review and meta-analysis that acupressure practices increase sleep quality (5). In a different systematic review, it was shown that 58.3% of relevant studies indicated that hypnosis had a positive influence on sleep results (6). It was also stated that, compared to the control group, the cupping procedure combined with acupuncture practice was superior in eliminating insomnia for patients with moderate insomnia (7). Li et al. determined that low doses of ozone therapy improved sleep quality parameters (4). It was seen that music therapy, massage, and therapeutic touch applied for critically ill patients increased their sleep quality (8). Gooneratne determined that complementary and alternative medicine treatments such as tai chi, acupuncture, acupressure, yoga, and meditation improved sleep parameters (9). The research in the literature to date has explored the effects of traditional and complementary treatments on sleep problems experienced by patients who underwent those treatments specifically due to their sleeping problems. However, no studies were encountered in the literature on the effects of traditional and complementary treatments on sleeping problems experienced by patients who underwent those procedures due to other health problems. In the

present study, the sleep quality and the factors affecting it among patients who received traditional and complementary treatments due to various health issues were examined. It should be noted that low sleep quality can increase the severity of existing health problems and can cause new health problems.

In this context, it is important that healthcare professionals be familiar with the sleep quality of their patients and the factors that affect it so that they can improve the patients' sleep quality and avoid the exacerbation of existing health problems or the occurrence of new ones.

METHOD

Study Design

This study, which aimed to determine sleep quality and the factors affecting it among patients who presented to a traditional and complementary medicine centre, was designed as a cross-sectional study. The STROBE checklist was applied in the reporting of the findings.

Sampling Method

The study's target population was patients presenting to a traditional and complementary medicine centre with any health issues. A random sampling method was used. The study's inclusion criteria were consent to participate, age of ≥18 years, not having any communication problems, and having presented to the traditional and complementary medicine centre. The study's exclusion criteria were age of <18 years, pregnancy, visual impairments, and cognitive disorders.

The G*Power-3.1.9.2 program was used to determine the sample size, which was calculated as a minimum of 131 for power of 0.95 (1-β) at α=0.05 assuming a standardized effect size of 0.29 based on the study of author's name.10 Subsequently, 314 patients were enrolled in the study.

Ethical Consideration

Ethics committee approval (E-71522473-050.01.04-146224-182) was obtained before the study began. The participants were informed about the study in accordance with the Declaration of Helsinki and their consent was obtained online via an informed consent form. All participants were enrolled in the study on a voluntary basis.

Data Collection

Data were collected with a survey conducted via Google Forms in June-December 2022.

Measures

Data were collected using a personal information form, the Cumhuriyet Subjective Sleep Quality Scale, and the Sleep Hygiene Index. Permission to use the scales was obtained via e-mail from the authors who developed them.

The personal information form included various questions regarding age, gender, marital status, health, and sleep.

The Cumhuriyet Subjective Sleep Quality Scale was developed by Sarıçam (11). This scale consists of 18 items and three subdimensions (psychosomatic effects, sleeping process, and sleep satisfaction). Items 3, 10, 11, 15, and 17 are reverse-coded. The scale is a four-point

Likert-type scale (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Frequently). As the scores obtained from the scale increase, sleep quality is considered to decrease. Sarıçam found the scale to have a Cronbach α value of 0.91. In this study, the Cronbach α value was 0.92 (11).

The Sleep Hygiene Index was developed by Mastin et al.12 The validity and reliability of the index's Turkish version were confirmed by Güzel Özdemir et al. (13). The index consists of 13 items and is a 5-point Likert-type scale (1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Frequently, 5 = Always). The lowest possible score is 13 and the highest is 65. High scores indicate worse sleep hygiene practices. The Cronbach α value was found to be 0.70 in the study conducted by Güzel Özdemir et al. (13). In this study, the Cronbach α value was 0.71.

Data Analysis

IBM SPSS Statistics 24 was used to analyse the data. Numbers and percentage ranges were calculated for the participants' personal information. Cronbach α coefficients were calculated for internal consistency. Spearman correlation was used in order to identify the relationship between the Cumhuriyet Subjective Sleep Quality Scale and Sleep Hygiene Index. Normality testing was performed to determine the tests to be applied in evaluating the collected data. As the normality test results showed that the scores for the Cumhuriyet Subjective Sleep Quality Scale and Sleep Hygiene Index were not normally distributed, the nonparametric Mann-Whitney U and Kruskal-Wallis H tests were used to analyse the data.

RESULTS

A total of 314 patients presenting to a traditional and complementary medicine centre were included in this study. The mean age of the patients was 44.89±11.86 years and 71.7% were women. The demographic characteristics of the patients are given in Table 1.

Table 1. Demographic Characteristics of the Study Sample, *N*=315

Variable	*N*	%
Age **44.89±11.86 years (min: 18, max: 86)**		
BMI **27.65±6.82**		
Gender		
Female	225	71.7
Male	89	28.3
Marital status		
Single	49	15.6
Married	265	84.4
Income		
Good	84	26.8
Medium	219	69.7
Low	11	3.5
Working status		
Worker	172	54.8
Not employed	113	36
Retired	29	9.2
Work schedule		
Starts in the morning	287	91.4
Shift worker	27	8.6
Smoking		
Yes	48	15.3
No	266	84.7
Exercise		
Yes	129	41.1
No	185	58.9

It was determined that 18.8% of the patients presented to the traditional and complementary medicine centre due to musculoskeletal system problems, 6.4% due to the gastrointestinal system, 3.8% due to the cardiovascular system, 14% due to the nervous system, 2.9% due to gynaecological problems, 4.5% due to psychological problems, 2.2% due to insomnia, 8.3% due to obesity and metabolic problems, 32.2% due to pain, and 7% due to other problems (allergies, restless leg syndrome, urticaria, wounds, fatigue, oedema, cancer, bruxism, acne, asthma, sweating, uveitis, overactive bladder, dementia, and eczema). Furthermore, 38.2% of the patients stated that their sleep had improved compared to before after receiving traditional and complementary treatment (Table 2).

Table 2. Reasons for Patients to Present to the Traditional and Complementary Medicine Centre and Characteristics of Their Sleep, *N*=315

Variable	*N*	%
Reasons for patients to present to the traditional and complementary medicine centre		
Musculoskeletal system problems	59	18.8
Gastrointestinal system problems	20	6.4
Cardiovascular system problems	12	3.8
Nervous system problems	44	14
Women's health problems	9	2.9
Psychological problems	14	4.5
Insomnia	7	2.2
Obesity and metabolic problems	26	8.3
Pain	101	32.2
Other problems	22	7
Daily sleep duration		
4-7 hours	154	49
>7 hours	160	51
Consumption of tea/coffee before bed		
None	128	40.8
1-3 cups	109	34.7
3-5 cups	77	24.5
Sleep quality before receiving traditional and complementary treatment		
Good	121	38.5
Moderate	116	36.9
Low	77	24.5
Sleep quality after receiving traditional and complementary treatment		
No changes	194	61.8
Better compared to before	120	38.2

It was determined that 82.2% of the patients underwent acupuncture, 12.7% hypnotherapy, 70.4% cupping therapy, 6.7% ozone therapy, 22.3% mesotherapy, 19.4% hirudotherapy, and 5.8% other alternative treatments (phytotherapy, homeopathy, osteopathy, prolotherapy, and reflexology).

Most of the patients who underwent acupuncture (31%), cupping therapy (33.9%), mesotherapy (37.1%), hirudotherapy (31.1%), reflexology (75%), and phytotherapy (42.9%) were patients suffering pain. Most patients who underwent hypnosis (17.5%) and all patients undergoing prolotherapy had musculoskeletal system problems. While 33% of patients who underwent homeopathic treatment had insomnia, 33% suffered from pain and 33% had obesity and metabolism-related problems. Finally, 2.2% of the patients presented to the traditional and complementary medicine centre with insomnia complaints and 1.6% of those patients underwent acupuncture, 5% hypnosis, 2.3% cupping therapy, and 33.3% homeopathy.

The median score of the patients according to the Cumhuriyet Subjective Sleep Quality Scale was 22 (IQR: 19). The median scores obtained for the subdimensions of psychosomatic effects, sleep duration, and sleep satisfaction were 7.00 (6.00), 7.00 (7.00), and 7.00 (7.00), respectively. The median Sleep Hygiene Index score of the patients was 25.00 (8.00). Spearman correlation was used to evaluate the relationship between the Cumhuriyet Subjective Sleep Quality and Sleep Hygiene Index and a positive relationship was found (rs=0.436, p=0.000).

Table 3. Variables Affecting Sleep

Characteristics	Cumhuriyet Subjective Sleep Quality Scale Median (IQR)	Sleep Hygiene Index Median (IQR)
Gender		
Female	24.00 (20.50)	26.00 (8.00)
Male	20.00 (17.50)	24.00 (8.00)
	z=-2.348 p=0.019	z=-2.007 p=0.045
Marital status		
Single	25.00 (19.50)	27.00 (6.50)
Married	22.00 (18.00)	25.00 (8.00)
	z=-0.612 p=0.541	z=-2.488 p=0.013
Income		
[a]Good	16.00 (18.00)	25.00 (7.00)
[b]Medium	23.00 (19.00)	25.00 (8.00)
[c]Low	31.00 (16.00)	29.00 (13.00)
	χ^2=12.347 p=0.002	χ^2=4.320 p=0.115
	a<b p=0.023 a<c p=0.009	
Work schedule		
Starts in the morning	22.00 (19.00)	25.00 (8.00)
Shift worker	22.00 (21.00)	27.00 (6.00)
	z=-0.98 p=0.922	z=-2.006 p=0.045
Daily sleeping duration		
4-7 hours	26.50 (23.00)	25.00 (7.00)
>7 hours	21.00 (16.00)	25.00 (8.75)
	z=-2.844 p=0.004	z=-0.384 p=0.701
Smoking		
Yes	26.00 (20.00)	26.50 (7.00)
No	21.50 (18.25)	25.00 (8.00)
	z=-1.910	z=-2.090
	p=0.056	p=0.037
Sleep quality before receiving traditional and complementary treatment		
[a]Good	14.000 (10.00)	23.000 (7.00)
[b]Medium	28.500 (14.00)	26.000 (7.00)
[c]Low	31.000 (21.00)	27.000 (8.50)
	χ^2=74.664 p=0.000	χ^2=26.583 p=0.000
	a<b p=0.000 a<c p=0.000	a<b p=0.000 a<c p=0.000

IQR: Interquartile Range.

Women's Cumhuriyet Subjective Sleep Quality Scale and Sleep Hygiene Index scores were statistically significantly higher compared to men (p<0.05). While Cumhuriyet Subjective Sleep Quality Scale scores did not show a statistically significant difference regarding marital status (p>0.05), unmarried people had statistically significantly higher Sleep Hygiene Index scores (p<0.05). Compared to those with medium and lower income status, people with higher incomes had statistically significantly lower Cumhuriyet Subjective Sleep Quality Scale scores (p<0.05). Shift workers had higher Sleep Hygiene Index scores (p<0.05). Patients who

reported having sleeping problems had higher Cumhuriyet Subjective Sleep Quality Scale and Sleep Hygiene Index scores ($p<0.05$). People sleeping 4-7 hours a day had statistically significantly higher Cumhuriyet Subjective Sleep Quality Scale scores compared to those sleeping ≥7 hours. Finally, the Cumhuriyet Subjective Sleep Quality Scale and Sleep Hygiene Index scores of patients who stated that their sleep quality was good before undergoing traditional and complementary treatment were lower compared to those with medium and poor sleep quality ($p<0.05$) (Table 3).

It was reported by 42.6% of the patients treated with acupuncture, 37.5% of the hypnosis patients, 40.3% of the cupping patients, 52.4% of the ozone therapy patients, 42.9% of the mesotherapy patients, 47.5% of the hirudotherapy patients, 66.7% of the prolotherapy patients, 75% of the reflexology patients, 100% of the osteopathy patients, 66.7% of the homeopathy patients, and 28.6% of the phytotherapy patients they had much better sleep after undergoing these treatments (Table 4).

Table 4. Sleep Quality of Patients After Undergoing Traditional and Complementary Treatment

	No changes	Better compared to before
Type of treatment	***N* (%)**	***N* (%)**
Acupuncture	148 (57.4)	110 (42.6)
Hypnosis	25 (62.5)	15 (37.5)
Cupping therapy	132 (59.7)	89 (40.3)
Ozone therapy	10 (47.6)	11 (52.4)
Mesotherapy	40 (57.1)	30 (42.9)
Hirudotherapy	32 (52.5)	29 (47.5)
Prolotherapy	1 (33.3)	2 (66.7)
Reflexology	1 (25)	3 (75)
Osteopathy	0 (0)	1 (100)
Homeopathy	1 (33.3)	2 (66.7)
Phytotherapy	5 (71.4)	2 (28.6)

DISCUSSION

Sleep quality affects physical and mental health. Impaired sleep quality can lead to various new health problems, increases in the severity of existing health issues, decreased productivity, and an increased likelihood of accidents. Accordingly, understanding sleep quality and the factors that affect it are crucial in eliminating those adverse outcomes (14).

In a broad sense, it was determined in the present study that the sleep quality and sleep hygiene of the participants were good. Overall, 38.2% of these patients reported that their sleep was better after receiving traditional and complementary treatments compared to the period before treatment. More specifically, 42.6% of those treated with acupuncture, 37.5% treated with hypnosis, 40.3% with cupping, 52.4% with ozone therapy, 42.9% with mesotherapy, 47.5% with hirudotherapy, 66.7% with prolotherapy, 75% with reflexology, 100% with osteopathy, 66.7% with homeopathy, and 28.6% with phytotherapy stated that, compared to before, they had much better sleep after undergoing these treatments.

Similar to our study, other researchers have concluded that acupuncture affects the sleeping process (15-17). Acupuncture was found to improve sleep quality by affecting neurotransmitter levels and regulating the biological clock (16).

It was stated that hypnosis could be used for sleeping problems because it can cause relaxation, increase suggestibility, enable access to preconscious levels of the mind and emotions, and permit cognitive reconstruction (18). In the present study, 37.5% of those who underwent hypnotherapy stated that their sleep was better after treatment. A systematic review

found that 58.3% of relevant studies showed that hypnosis benefited sleep quality, 12.5% reported mixed results, and 29.2% indicated no benefits (6).

In this study, 40.3% of those who underwent cupping therapy stated that their sleep was much better compared to before. It was indicated in another study that cupping therapy applied along with acupuncture was superior for patients with moderate insomnia (7).

We found that 52.4% of the patients who underwent ozone therapy considered their sleep quality to be much better compared to before. It was previously revealed that low doses of ozone therapy improved sleep quality parameters (4).

Among patients who underwent mesotherapy, 42.9% stated that, compared to before, their sleep was much better. Sleep quality among patients who underwent mesotherapy could have improved because most of the people receiving mesotherapy (37.1%) suffered from pain, which the treatment successfully addressed. It was previously shown that as pain decreased, the sleep quality of patients increased (19). Therefore, it is not surprising that sleep was improved among patients whose pain was relieved.

In this study, most patients who underwent hirudotherapy also complained about pain and also reported that their sleep improved. It was suggested in the literature that hirudotherapy can be used against pain, as pain may be alleviated by anaesthetic substances in the saliva of leeches (20). Another study showed that hirudotherapy decreased the severity of joint pain (21). Similarly, in our study, patients slept better after pain relief via hirudotherapy.

In the present study, the percentage of patients presenting to the traditional and complementary medicine centre with insomnia was rather low, but among those patients, 33.3% underwent homeopathy. It was suggested in a randomized controlled study that homeopathy was effective in treating sleeping disorders (22). However, another systematic review showed that homeopathy was not an effective treatment method for insomnia and disorders related to sleep (23). Randomized controlled studies with larger samples are required in this regard.

It was revealed in the present study that as sleep hygiene increased, so did sleep quality. A previous study found that sleep hygiene practices are significant variables that affect sleep quality (24). The concept of sleep hygiene behaviour was first introduced by Peter Hauri (25). Behaviours that promote good sleep are accepted as sleep hygiene. Ensuring regular sleeping and waking hours, keeping bedrooms comfortable and silent, avoiding occasional naps, not performing challenging tasks in the bedroom, and avoiding caffeine, nicotine, and alcohol before bed are some examples of sleep hygiene behaviours (26). It is expected that practicing these behaviours can increase sleep quality.

The present study showed that women had poorer sleep quality and sleep hygiene compared to men. Similar results were previously obtained (27,28). In another study, on the other hand, it was revealed that gender did not affect sleep quality (29). The reason why women had poorer sleep quality and sleep hygiene in our study may be that most of the participants were women (71.7%), the study was conducted with people who had various diseases, and women have more household responsibilities in Turkish society compared to men, such as child care, cooking, and household chores.

Marital status was found not to affect sleep quality in this study. However, compared to married individuals, unmarried individuals had poorer sleep hygiene. Similarly, Deniz Doğan

et al. concluded that marital status did not affect sleep quality (30). In another study, compared to unmarried individuals, married individuals had better sleep quality (31). The differences in our study could have arisen from the fact that research was carried out on individuals with different diseases.

It was revealed in this study that, compared to those with medium and lower income statuses, patients with higher incomes had better sleep quality. Similarly, it was previously determined that individuals with medium income status had poorer sleep quality compared to those with high income status (32). On the other hand, a study of patients with heart failure concluded that income level did not affect sleep quality (33). The difference in our study might have arisen from the fact that all patients included in the study had undergone traditional and complementary treatment at least once in their lifetimes regardless of income status.

Shift work is becoming more and more prevalent in today's world. Shift workers sleep at unusual hours. It was revealed in this study that patients who began work in the morning had better sleep hygiene than shift workers did. In another study, it was suggested that shift work affected life quality and had an adverse impact on sleep schedules; shift workers frequently consumed caffeine as a fatigue management strategy (34).Poorer sleep hygiene among shift workers compared to others might have arisen from the increased consumption of tea and coffee and disturbance of biological rhythms and traditional sleep patterns.

It was determined in this study that patients sleeping 4-7 hours a day had poorer sleep quality compared to those sleeping more than 7 hours. Generally, 7.5-8 hours of nightly sleep is said to be sufficient for adults (35). It was found in another study that sleeping less or more than this standard recommended amount adversely affects sleep quality (36). Our results support those findings.

This study had some limitations. The first limitation was that the information collected on sleep quality and hygiene was based on participants' self-assessments. The second limitation was that the research was conducted in a single centre. Therefore, the results of this study cannot be generalized across wider geographic areas. The third limitation was that data were collected online. The fourth limitation was the study's cross-sectional nature; therefore, we cannot offer objective implications. The fifth limitation was the inability to measure patients' sleep quality and sleep hygiene both before and after they presented to the traditional and complementary medicine centre.

It can be suggested that further studies conducted with patients treated at traditional and complementary medicine centres evaluate the severity of the patients' health problems and identify the relationship between severity and sleep. This would make it possible to identify whether sleep quality improves thanks to the applied treatment or the treatment of already existing diseases.

CONCLUSION

This study has shown that the sleep quality and hygiene of patients presenting to a traditional and complementary medicine centre were both generally good.

The participating patients, who presented to the centre due to various health problems, had improved sleep after receiving traditional and complementary treatments. Specifically, individuals who received acupuncture, hypnotherapy, cupping therapy, ozone therapy, mesotherapy, hirudotherapy, prolotherapy, reflexology, osteopathy, phototherapy, and homeopathy treatments had improved sleep compared to the period before these treatments.

Gender affected both sleep quality and sleep hygiene. While the daily duration of sleep and income status affected sleep quality, marital status and type of work affected sleep hygiene. Finally, it was seen that sleep hygiene increased sleep quality.

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The Relationship Of Suicide Risk With Cognitive Flexibility And Social Cognition In Patients With Obsessive Compulsory Disorder

Obsesif Kompulsif Bozukluk Tanılı Hastalarda İntihar Riskinin Bilişsel Esneklik Ve Sosyal Biliş İle İlişkisinin Değerlendirilmesi

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Abstract

Objective: There is a relationship between disease severity and suicide risk in individuals diagnosed with obsessive-compulsive disorder.Within the scope of this research, we aimed to elucidate the importance of treatments aimed at improving social cognitive skills and cognitive flexibility in preventing suicide by evaluating the effect of social cognition and cognitive flexibility on suicide risk in obsessive-compulsive disorder in a descriptive setting.
Method: Thisprospective, descriptive, cross-sectional studywas conducted by face-to-face survey and data collection method. A total of 51 patients aged between 18 and 65, diagnosed with OCD according to DSM–5 criteria were randomized in this research. Yale-Brown Obsession Compulsion Scale(Y – BOCS), Suicide Probability Scale(SPS), Cognitive Flexibility Inventory(CFI), Implicit Test, and Reading Mind from Eyes Test(RMET) were applied to the study participants.
Results: When sociodemographic and clinical data were compared with SPS, suicidal ideation and suicide attempt, no statistically significant difference was found ($p>0.05$). A positive correlation was found between the Y-BOCS scale and the SPS total and subscales. This correlation was statistically significant ($p<0.05$). A negative correlation was found between the Y-BOCS scale and CFI, and a negative correlation was found between the total subscales of the SPS and CFI($p<0.05$). The CFI scores of people with past suicidal ideation were found to be low ($p<0.05$). No statistically significant relationship was found between social cognition assessment scales and SPS ($p>0.05$).
Conclusion: Our study observed that the severity of obsessions and compulsions increased with low cognitive flexibility. Cognitive rigidity can also increase the risk of suicide by increasing the severity of the disease. A significant negative correlation exists between suicidal ideation and cognitive flexibility in OCD patients. It has been evaluated that therapeutic interventions to cognitive flexibility will contribute positively to suicide risk and disease prognosis.

Keywords: Obsessive-Compulsive Disorder, Cognitive Flexibility, Suicide.

Özet

Amaç: Obsesif kompulsif bozukluk tanılı bireylerde hastalık şiddeti ile intihar riski arasında ilişki vardır. Bu araştırma kapsamında sosyal biliş ve bilişsel esnekliğin obsesif kompulsif bozuklukta intihar riskine etkisini betimsel bir ortamda değerlendirerek sosyal bilişsel becerileri ve bilişsel esnekliği geliştirmeye yönelik tedavilerin intiharı önlemedeki önemini ortaya koymayı amaçladık.
Yöntem: Bu prospektif, tanımlayıcı, kesitsel araştırma, yüz yüze anket ve veri toplama yöntemiyle yapılmıştır. Bu araştırmada DSM-5 kriterlerine göre OKB tanısı almış, yaşları 18 ile 65 arasında değişen toplam 51 hasta randomize edilmiştir. Çalışmaya katılanlara Yale-Brown Obsession Compulsion Scale (Y – BOCS), İntihar

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Olasılığı Ölçeği (İOÖ), Bilişsel Esneklik Envanteri (BEE), Örtük Test ve Gözlerden Zihin Okuma Testi (GZOT) uygulandı.
Bulgular: İOÖ, intihar düşüncesi ve intihar girişimi ile sosyodemografik ve klinik veriler karşılaştırıldığında istatistiksel açıdan anlamlı bir fark görülmemiştir (p>0,05). Y-BOCS ölçeği ile İOÖ total ve alt ölçekleri arasında pozitif korelasyon saptanmıştır. Bu korelasyon istatistiksel olarak anlamlı ölçülmüştür (p<0,05). Y-BOCS ölçeği ile BEE arasında negatif korelasyon, İOÖ total ve alt ölçekleri ile BEE arasında da negatif korelasyon saptanmıştır (p<0,05). Geçmiş intihar düşüncesine sahip kişilerin BEE skorları düşük olarak saptanmıştır (p<0,05). Sosyal biliş değerlendirme ölçekleri ile İOÖ arasında istatistiksel olarak anlamlı bir ilişki saptanamamıştır (p>0,05).
Sonuç: Obsesif kompulsif bozuklukta bilişsel esnekliğin az olması ile, hastalık şiddetinin ve intihar olasılığının yüksek olması arasında ilişki saptanmıştır. Hastalık şiddetinin intihar olasılığını artırmasında bilişsel katılığın aracı rol üstlendiği düşünülmüştür. Bilişsel esnekliğe yapılacak terapötik müdahalelerin intihar riski ve hastalık prognozuna olumlu katkı yapacağı değerlendirilmiştir.

Anahtar Kelimeler: Obsesif Kompulsif Bozukluk, Bilişsel Esneklik, İntihar.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental disorder first described in the 19th century, characterized by obsessions, compulsions, or both. Obsessions are impulses, phantasies, or thoughts that repeatedly enter a person's mind, that cannot be dismissed by conscious effort, and that cause discomfort (1). Compulsions are behaviors or mental acts that a person does to neutralize obsessions. Although compulsions initially relieve the anxiety caused by the obsessions, they can also cause anxiety and distress throughout the disease. Obsessions and compulsions are alien to one's self, that is, ego-dystonic. OCD, like other mental disorders, causes loss of time and leads to impairments in social, occupational, and other important areas of functioning (2).

OCD is one of the most common mental disorders. As a result of studies conducted in different continents, the lifetime prevalence rate is thought to be 2 – 3%. Obsessive-compulsive disorder (OCD), described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM – 5), can be defined as the physical and mental actions taken to reduce obsessions and the anxiety they cause. It is defined by the co-existence of compulsions and significant loss of functionality due to obsessions and compulsions (3).

Obsessions and compulsions may vary according to age, gender, and genetic characteristics. The most common obsessions in adults are, in order, contagion, suspicion (skepticism), somatic obsessions, symmetry, aggression and sexual obsessions. The most common compulsions are in order; checking, washing, counting, verification, symmetry, and order, stacking. Contagion obsession is the most common type.Recent studies indicate that OCD increases the risk of suicide independently of other factors (2,4).

It is stated that cognitive functions are impaired in OCD patients compared to the healthy population. Although cognitive skills are not included in the diagnostic criteria of OCD, they significantly affect functionality and disease severity. The most researched cognitive functions in OCD are; short-term memory, executive functions, decision-making, attention, verbal fluency, and verbal memory (5). Many psychiatric disorders are characterized by impairments in the ability to successfully and meaningfully interact with people. Therefore, describing the social difficulties observed in psychiatric disorders as social cognition disorders gives us a new dimension of thought. One of the diseases in which social cognitive abilities are most impaired is obsessive-compulsive disorder (6).

There is a relationship between disease severity and suicide risk in individuals diagnosed with obsessive-compulsive disorder. Decreased cognitive flexibility; It increases the risk of suicide in obsessive-compulsive disorder patients. Social cognitive disability; increases the risk of suicide in obsessive-compulsive disorder patients (7).

In previous literature, there are studies on the effect of social cognition on the severity of OCD, but there is no study investigating its effect on suicide risk. At the same time, the effect of cognitive flexibility, which is a sub-branch of executive functions, on suicide risk in OCD has been separately studied in limited numbers in the literature (8). Within the scope of this research,we aimed to elucidate the importance of treatments aimed at improving social cognitive skills and cognitive flexibility in preventing suicide by evaluating the effect of social cognition and cognitive flexibility on suicide risk in obsessive-compulsive disorder in a descriptive setting.

METHOD

This is a prospective, descriptive, and cross-sectional study. It was conducted by face-to-face survey and data collection method. It was carried out between 1 May 2022 and 1 November 2022 in Balıkesir University Faculty of Medicine, Department of Psychiatry Outpatient Clinic and Clinic. A total of 51 OCD patients were randomized. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution on 22.03.2022 with protocol number 20224/37, andinformed consent has been obtained from all participants.

Patients aged between 18 and 65, diagnosed with OCD according to DSM–5 criteria, and who completed at least five years of primary education were randomized in this research.Yale-Brown Obsession Compulsion Scale (Y – BOCS), Suicide Probability Scale(SPS), Cognitive Flexibility Inventory (CFI), Implicit Test, and Reading Mind from Eyes Test (RMET) were applied to the study participants.

In order to determine the study group, the sample size was determined through the G-Power 3.1 program. The statistical significance level was accepted as α=0.05, and the power of the study was 80%. With this method, it was decided to include a minimum of 47 patients in the study.

Statistical Analysis

Statistical analyzes were performed using SPSS version 26 software. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov- Smirnov/ Shapiro-Wilk tests). Descriptive analyzes were given using mean and standard deviations for parametric variables. Student T-test and One Way ANOVA (post hoc Bonferroni) were preferred for parametric quantitative data for independent groups. Mann-Whitney U Test was preferred for non-parametric quantitative data when statistical significance was determined between two independent groups. Pearson Correlation Test was used to examine the correlation of parametric data, and Spearman Correlation Test was used for non-parametric data. Nominal data are given using crosstabs. The statistical significance level (p-value) was accepted as 0.05.

RESULTS

A total of 51 patients were included in this study. Twelve (23%) patients were male, and 39 (77%) were female. The mean age of the patients was 35.2±12.93 (minimum 18, maximum

64). It was determined that 66.6% of the patients had high school or higher education. A majority of the patients(80%) lived with their families, and 20% lived alone.

Table1. Correlation of Y-BOCS Scale with Other Scales

		Y-BOCS TOTAL	Y-BOCS OBSESSION	Y-BOCS COMPULSION
SPS –total	r	**0,388****	**0,346****	**0,348****
	p	**0,005****	**0,013****	**0,012****
	n	51	51	**51**
SPS – negative self-esteem	r	**0,417**	**0,376****	**0,414****
	p	**0,002****	**0,007****	**0,003****
	n	51	51	**51**
SPS – suicidal intention	r	**0,372****	**0,354****	**0,346****
	p	**0,007****	**0,011****	**0,013****
	n	51	51	**51**
SPS – hopelessness	r	**0,278****	0,239	**0,255**
	p	**0,049****	0,091	**0,071**
	n	51	51	**51**
SPS – hostility	r	0,174	0,19	**0,071**
	p	0,223	0,172	**0,622**
	n	51	51	**51**
Cognitive Flexibility	r	**-0,431****	**-0,398****	**-0,423****
	p	**0,002****	**0,004****	**0,002****
	n	51	51	**51**
Implicit Test	r	-0,032	-0,001	**-0,049**
	p	0,825	0,995	**0,561**
	n	51	51	**51**
RMET	r	-0,164	-0,108	**-0,225**
	p	0,251	0,452	**0,112**
	n	**51**	**51**	**51**

The previous psychiatric history of the patients revealed that 41.2% (n=21) had suicidal ideation in the past, and 9.8% (n=5) had a history of suicide attempts. Additionally, 17.6% (n=9) of the patients had suicidal ideation in their relatives,while 3.9% were in first-degree closeness, 9.8% were in second-degree closeness, and 3.9% were in the level of friends without any relationship.

Table 2. Correlations of SPS with Cognitive Flexibility

		SPS - hopelessness	SPS – suicidal intentions	SPS – hostility	SPS – Negative self-esteem	SPS – Total
Cognitive Flexibility Inventory	r	-0,181	-0,275	-0,139	-,301*	**-,326***
	p	0,204	0,051	0,33	0,032	**0,02**
	N	**51**	**51**	**51**	**51**	**51**

The mean OCD duration of the patients was 10.29±9.28 years(minimum1, maximum 40). In terms of medication, 11.8% (n=6) of the patients were not currently using drugs, 88.2%

(n=45) were using drugs, and the most commonly used drug was selective serotonin reuptake inhibitors (SSRIs)(43.1%).

The comorbid disease was detected in 25.5% of the patients, and no additional disease was detected in 74.5% of the patients. The most common comorbidity was hypertension, with a rate of 3.9%. It was determined that 13.7% of the patients were hospitalized and treated for psychiatric illnesses. It was shown that 86.3% did not have a history of hospitalization.

A positive correlation was found between Y-BOCS scale scores and SPS-total, SPS-negative self-perception, SPS-hopelessness, and SPS-suicidal ideation subscales. The differences between them were statistically significant (r=0.388, 0.417, 0.007) ($p<0.05$). A negative correlation was found between Y-BOCS scores and Cognitive Flexibility Inventory, and this correlation was statistically significant (r=- 0.431) ($p<0.05$). When the Y-BOCS scores were compared with the Implicit Test(IT), which measures social cognition, and the RMET scores, no statistical difference was found between them ($p>0.05$) (Table 1, Table 2, and Table 3).

Table 3. Correlations of the Suicide Probability Scale with RMET and implicit test

		SPS – hopelessness	SPS – suicidal intentions	SPS – hostility	SPS – Negative self-esteem	SPS – Total
RMET	r	0,107	0,022	0,158	-0,163	**0,06**
	p	0,454	0,878	0,267	0,254	**0,674**
	N	51	51	51	51	**51**
Implicity Test	r	0,129	-0,046	0,116	-0,115	**0,023**
	p	0,365	0,749	0,419	0,422	**0,875**
	N	**51**	**51**	**51**	**51**	**51**

A negative correlation was found between cognitive flexibility and SPS and its sub-categories, and the negative correlations with SPS-Total, and SPS-Negative Self-Perception were statistically significant (r=-0.326,-0.301) ($p<0.05$).

The relationship between suicidal ideation history and cognitive flexibility was examined. While the mean ±SD values of the Cognitive Flexibility Inventory were 10.91 for those with suicidal ideation (mean 60.75), it was calculated as 9.12 (mean 68.97) for those without suicidal ideation. A negative correlation was found between cognitive flexibility and suicidal ideation, and the difference between the two groups was statistically significant ($p<0.05$).

DISCUSSION

Previous literature elaborated that the risk of suicide in OCD patients was 3 times higher, and deaths due to suicide were 10 times higher compared to healthy individuals (9). According to published articles, 56% of OCD patients had a desire to die, 46% had thoughts of death, 20% had suicidal plans, and 10% were prepared to commit suicide (10). More than 90% of OCD patients had decreased self-esteem, 57% had suicidal ideation, and 12.2% had a history of suicide attempts. In a recent study conducted in 2022, lifetime thoughts of death in OCD were found to be 64.3%, and suicide attempts were found to be higher than expected, with 16.3% (11). Our study found that 41.2% of the patients had suicidal ideation, and 9.8% attempted suicide, consistent with the literature.

A study by Albert et al. found that the risk of suicide in OCD increased as the severity of obsessions and compulsions increased (12). Again, a recent meta-analysis stated that the risk

of suicide increases as the severity of obsessions increases (13). In our study, according to the literature, it was determined that as the Y-BOCS total and subscales scores increased, there was an increase in the SPS, which was found to be statistically significant.

Since the 2000s, the effects of executive functions on suicide have been investigated. In a study by Kim et al.on patients with schizophrenia, scores on psychomotor speed, attention, working memory, word memory, and executive functions were found to be higher in patients with a history of suicide than in patients without a history of suicide (14). Nangle et al. found that schizophrenic patients with better executive functions had more advanced suicide attempt planning skills (15). In the literature, when OCD patients are examined, it has been found that decision-making is impaired, and the decision-making time is prolonged, especially in cases of doubt and uncertainty. The effect of executive functions on the risk of suicide in OCD is also associatedwith past and active suicidal ideation and IOS scores decreased in OCD patients with high decision-making skills (16). Studies investigating the effects of cognitive flexibility defined under executive functions on suicide are limited. Impairments in cognitive flexibility are thought to lead to suicide, leading to mental illnesses such as major depressive disorder, OCD, and anorexia nervosa. Dickoff et al. stated that cognitive rigidity, inadequate problem-solving skills, and hopelessness can be seen together, which may be a predisposing factor to suicide (17).

Our study found a negative correlation between the cognitive flexibility inventory and the suicide probability scale total and negative self-perception subscale. Cognitive rigidity is thought to cause suicide by causing an exaggerated sense of responsibility, misinterpretation of meaning, and inability to develop alternative thoughts described in the cognitive model of obsessive-compulsive disorder. Differences between studies may be due to the sample size, the characteristics of the sample's diagnosis group, the socio-cultural and economic characteristics of the place where the study was conducted, the religious beliefs of the participants, and the different tests used. Our study determined that individuals with weak cognitive flexibility had a higher rate of past suicidal ideation. The same relationship was not found between suicide attempts and cognitive flexibility. This finding is thought to be consistent with previous studies (18). We think that our study is valuable in terms of investigating the risk of suicide in OCD, apart from cognitive flexibility and other executive functions.

Social isolation, deterioration in interpersonal interaction, social conflicts and separations, and loss of social support have an important place among the suicide risk factors determined by the World Health Organization(WHO) (19).The help-seeking behavior of individuals with weak social cognitive skills is thought to decrease, and the possibility of converting suicidal ideation into an attempt increases. The most studied area of social cognition is the theory of mind skills. Nestor et al. stated that the lack of theory of mind, which is defined as a negative perception of the thoughts and feelings of others, causes the person to see himself as a burden. On the contrary, some comments that seeing oneself as a burden may lead to disorders in the theory of mind. Despite two different interpretations, Nestor argues that excessive mentalization, which is considered a specific theory of mind disorder, increases suicidal ideation (20).

Considering the relationship between social cognition and suicide risk in psychiatric diseases, it was stated that weak social cognition functions increased the risk of suicide in patients with first-episode psychosis in 2022. This finding has explained that perceived social stress increases as a result of high sensitivity to social and emotional data, and the risk of suicide increases with disorders in stress management skills (17,21). Jollant et al. indicated the higher

imagination test scores in psychosis patients with a high risk of suicide to the increased sensitivity of individuals to social cues and verbal expressions (22).

Another group of diseases in which social cognition is frequently studied is depressive disorders. In a study with 189 participants in total, the severity of depression and face recognition test scores of students with and without active psychiatric complaints were compared. As the depression scores increased, difficulties in recognizing neutral and positive faces were detected. Negative schemas in depressed patients have been cited as the reason for this (23). Depressed patients describe neutral faces as sad and happy faces as neutral, no information was found in this study that defects in face recognition skills increase suicidal behavior. Depressed patients without suicidal behavior recognize negative faces as well as healthy controls, while the suicidal group has less success in recognizing negative faces. When the total scores were compared, the face recognition performance of the suicidal group was lower but not statistically significant (24). Szanto et al., on the other hand, compared depressed patients with and without suicide attempts and found a significant reduction in RMET scores in those who attempted suicide (25).

When OCD studies are analyzed, although it is seen that the importance of social cognition is neglected, chronic problems in social, cognitive, and emotional functions are stated in individuals with this disease. The fact that brain regions that provide social cognitive processes, such as the amygdala, anterior cingulate cortex, and insula, are also shown in the pathophysiology of OCD supports this relationship (26). Salazar et al.argue that with the development of social cognitive skills and social relations becoming one of the important issues in the prevention and treatment of OCD, treatment response will increase, and treatment discontinuation rates will decrease (27). Although social cognitive impairments are associated with decreased response to treatment, social cognition has not been specifically evaluated in OCD, and the disease's quality of life has generally been investigated (28).

Research on subtypes of social cognition, such as the theory of mind in OCD, is very scarce. Recent studies have reported low theory of mind skills in OCD (29). In 2022, Bora reported that in a meta-analysis study consisting of 1161 OCD patients and 1329 healthy controls, those with OCD showed theory of mind deficits (30). While Aigner et al. identified significant difficulty in recognizing sad faces in OCD, they found that neutral faces were evaluated as sad and happy faces as neutral or sad (31). In the study by Corcoran et al., OCD patients scored significantly lower than healthy controls in recognizing facial expressions of disgust (32).

Although social cognitive skills have been examined in many psychiatric diseases and suicide cases, no study has been found to evaluate the effect of social cognition on suicide risk in OCD. Our study found no significant relationship between the tests measuring social cognition and the suicidal probability scale total score and subscale values in OCD patients. Despite the knowledge that executive functions can affect social cognitive skills, the strength of our study was that RTOT is a test representing the emotional domain of social cognition and is not affected by executive functions. There was no significant relationship between past suicidal ideation and suicide attempt and social cognition tests. In our study, it was evaluated that social cognition had no effect on disease severity in OCD. This finding was considered among the reasons contributing to the lack of effect of social cognition on suicide risk. We think that the small sample size, the absence of active suicidal thoughts in the patients in our study, and the exclusion of the diagnosis of moderate to severe depressive episode were effective in our results. There is a need to repeat the tests with studies with large samples. The strengths of our study are that it is the first study in the literature on this subject, the diagnosis

of OCD is made in the presence of an experienced clinician, and the RMET is unaffected by executive dysfunctions.

CONCLUSION

Our study observed that the severity of obsessions and compulsions increased if cognitive flexibility was low. Cognitive rigidity can also increase the risk of suicide by increasing the severity of the disease. A significant negative correlation exists between suicidal ideation and cognitive flexibility in OCD patients. It has been evaluated that therapeutic interventions to cognitive flexibility will contribute positively to suicide risk and disease prognosis.

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Competing interests: The authors declare that they have no competing interests.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.Ethics committee approval has been granted from our institution.Informed consent has been obtained from all participants.

Abbreviations

CFI : Cognitive Flexibility Inventory

DSM – 5 : Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

IT : Implicit Test

OCD : Obsessive-compulsive disorder

RMET : Reading Minds from the Eyes Test

SD : Standard Deviation

SPS : Suicide Probability Scale

SPSS : Statistical Package for the Social Sciences

SSRI : Selective serotonin re-uptake inhibitor

WHO : World Health Organization

Y – BOCS : Yale-Brown Obsession Compulsion Scale

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Orthorexia Nervosa Tendencies of Liver Transplant Patients Receiving Immunosuppressant Treatment: A Cross-Sectional Study

İmmünsüpresan Tedavi Alan Karaciğer Nakli Hastalarının Ortoreksiya Nervoza Eğilimlerinin Belirlenmesi: Kesitsel Bir Çalışma

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Abstract

Objective: One of the most important factors after organ transplantation is immunotherapy, which is effective in reducing immune response to prevent post-transplant graft rejection, whileanother factor is a balanced nutrition. With these considerations in mind, this study aimed to determine the orthorexia nervosa tendencies of liver transplant patients receiving immunosuppressant treatment.
Method: This descriptive and cross-sectional study was carried out with patients who underwent liver transplantation at the liver transplantation institute of a university hospital in eastern Turkey. A sociodemographic information form and ORTO-R were used to collect data. The data were collected from patients who attended their follow-ups between May and August 2022.
Results: The mean age of the 176 patients who were receiving immunosuppressive treatment was 58.55±7.56, while 86.4% had not received any education on nutrition. The mean ORTO-R score of the patients was 17.09±2.70, which indicated moderate orthorexia. In our study, it was concluded that the majority of the patients who were using immunosuppressive medication had not received any education on nutrition, and they were moderately orthorexic.
Conclusion: It should be kept in mind that this obsessive form of eating will affect balanced nutrition among patients who have gone through a major transplant process. To make the drug-diet interaction in patients using immunosuppressive drugs after organ transplantation beneficial, ensure that they have a sufficient and balanced diet, and make this diet sustainable, it is important to monitor these patients. Additionally, it is thought that evaluating the pre-transplant orthorexia nervosa tendencies of advanced-stage liver transplant patients will increase post-transplant success.

Keywords: Immunosuppressive Therapy, Liver Transplantation, Nutrition, Orthorexia Nervosa, Nutrition education.

Özet

Amaç: Nakil sonrası greft rejeksiyonunun önlenebilmesi ve organ fonksiyonunun korunması için immün yanıtın azaltılmasında etkili immünoterapi nakil sonrası bakımın en önemli faktörlerden biri iken, bir diğer faktör ise dengeli beslenmedir. Bu düşüncelerden yola çıkarak, bu çalışma immünsüpresan tedavialan karaciğer nakli hastalarının ortoreksiya nervoza eğilimlerini belirlemeyi amaçladı.
Yöntem: Bu tanımlayıcı ve kesitsel çalışma, Türkiye'nin doğusunda bir üniversite hastanesinin karaciğer nakli enstitüsünde karaciğer nakli yapılan hastalarla yapıldı. Verilerin toplanmasında sosyodemografik bilgi formu ve ORTO-R kullanıldı. Veriler, Mayıs-Ağustos 2022 tarihleri arasında poliklinik takiplerine gelen hastalardan toplandı.

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Bulgular: İmmünsüpresif tedavi alan 176 hastanın yaş ortalaması 58,55±7,56 iken, %86,4'ü beslenme konusunda herhangi bir eğitim almamıştı. Hastaların ortalama ORTO-R skoru 17,09±2,70 olup orta derecede ortoreksiyaya işaret etmektedir. Çalışmamızda immünsüpresif ilaç kullanan hastaların büyük çoğunluğunun beslenme konusunda herhangi bir eğitim almadıkları ve orta derecede ortoreksik oldukları sonucuna varıldı.
Sonuç: Bu takıntılı yeme şeklinin, büyük bir nakil sürecinden geçmiş hastalarda dengeli beslenmeyi etkileyeceği akılda tutulmalıdır. Organ nakli sonrası immünsüpresif ilaç kullanan hastalarda ilaç-diyet etkileşiminin faydalı olabilmesi, yeterli ve dengeli beslenmelerinin sağlanması ve bu diyetin sürdürülebilir olabilmesi için bu hastaların izlenmesi önemlidir. Ayrıca ileri evre karaciğer nakli hastalarının nakil öncesi ortoreksiya nervoza eğilimlerinin değerlendirilmesinin nakil sonrası başarıyı artıracağı düşünülmektedir.

AnahtarKelimeler: İmmünsüpresif Tedavi, Karaciğer Nakli, Beslenme, Ortoreksiya Nervoza, Beslenme eğitimi.

INTRODUCTION

Liver transplantation refers to the transplantation of a graft liver from a live/cadaveric donor with blood-tissue compatibility with an end-stage liver failure patient to increase their life expectancy and quality in cases where there is no chance of success with medical treatment (1, 2). However, the detection of the graft by the immune system as a foreign body and the immune response to destroy the transplanted organ may lead to severe dysfunction in the transplanted liver and the rejection of the liver (3, 4). For this reason, to prevent post-transplant graft rejection and preserve organ function in liver transplant cases, immunosuppressive drugs that suppress the immune system are used. In this sense, one of the most important factors in post-transplant care is immunotherapy, which is effective in reducing immune response (4, 5). Another factor that speeds up graft survival and the adjustment process after transplantation is balanced nutrition. To speed up the adjustment process, increase the quality of life of advanced-stage liver disease patients and prevent diet-related complications, the nutritional statuses of these patients should be assessed as soon as possible in the pre-transplant phase, and the appropriate dietary interventions should be made (6). According to previous studies, dietary intake in liver transplant patients increases significantly after their transplant operation. This issue is more noticeable especially among individuals who had undergone severe dietary restrictions before their transplant and suffered from pre-transplant gastrointestinal symptoms and anorexia (7, 8). There are many factors that affect sufficient and balanced nutrition after transplant operations. These factors include perioperativemalnutrition, surgicalstress, immunosuppressivetreatment, energy metabolism, socioculturalstatus, and postoperative complications (9-11).

The term “orthorexia” emerged in 1997, and it was derived from the Greek words “ortho” meaning “right, proper” and “orexis”meaning “appetite” (12, 13). Orthorexianervosa (ON) is defined as an obsession with proper eating, and orthorexic individuals are more interested in the quality of their food than in its quantity (13-17). They keep busy with planning their foods, avoiding foods that are considered impure or unhealthy, checking their food sources, and following up on all food-related concerns such as packaging, processing, and the inclusion of artificial sweeteners. Moreover, they consider it necessary to constantly comply with rules about preparing food, consuming food, and healthy eating, and they aim to never break a rule. In these patients, nutritional deficiencies, severe weight loss, and similar medical complications associated with the avoidance of some food groups may develop. Furthermore,

as a consequence of withdrawal from social contexts, they may also experience educational and occupational issues, as well as social isolation (13-17).

Data on the prevalence of ON have been collected in studies conducted with various populations including medical students, high school students, artists, and dieticians (18). No study examining orthorexia nervosa in patients using post-transplant immunosuppressives could be found.

The purpose of this study is to determine the orthorexia nervosa tendencies of liver transplant patients receiving immunosuppressanttreatment.

METHOD

Design and Participants

This descriptive and cross-sectional study was carried out with patients who underwent liver transplantation at the liver transplantation institute of a university hospital in eastern Turkey. The population of the study included patients who had undergone liver transplantation in the last 2 years. For 321 patients, using the formula for a known population[$n= N.t^2 p.q / (d^2.(N-1) + t^2 p.q$], with the parameters $\alpha= .05$, $p= .5$, and $q= .5$, with $d= .05$ error, and in a 95% confidence interval, the minimum required sample size was calculated as 176(19). The inclusion criteria were being at or over the age of 18, having undergone liver transplantation in the last 2 years with at least 6 months since transplantation, and voluntarily agreeing to participate in the study. The exclusion criteria were being under the age of 18, having undergone liver transplantation more than 2 years ago, and not agreeing to participate in the study.

Data Collection Instruments

A “sociodemographicinformation form” and “ORTO-R” were used for data collection.

Sociodemographic Information Form

The form included questions on the patients’ age, sex, education level, marital status, income level, occupation, family structure, type of transplant, nutritional education status, time of transplant, and access to nutrition-related information sources.

ORTO-R scale

The ORTO-R is a revised version (14) of the ORTO-15 scale, showing an unstable factorial structure, and is a scale used to assess individuals' pathological obsessions for healthy food (14,20). The validity and reliability study of the ORTO-15 scale in Turkey was conducted by Arusoğlu(21), and the ORTO-R questions consisting of 6 items (3, 4, 7, 10, 11, 12) of the ORTO-15 scale (20) range from "always" to "never". It is a 4-point Likert-type scale with varying degrees of variation (14, 20) According to the most recent studies, the ORTO-R scale is a more reliable scale than ORTO-15 to evaluate and compare orthorexic trends in different populations (22). A minimum of 6 points from the ORTO-R scale and a maximum score of 24. In the ORTO-R, low scores represent low levels of orthorexic eating behavior and high

scores represent high levels of orthorexic eating behavior (14). In this study, the Cronbach alpha internal consistency coefficient of the ORTO-R scale was found to be 0.81.

Data Collection

The data of the study were collected from liver transplant patients who met the inclusion criteria and presented to the organ transplantation outpatient clinics of the liver transplantation institute where the study was conducted between May and August 2022.

Statistical Analysis

The data that were collected in the study were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, Version 25, Armonk, NY: IBM Corp. Released 2017).Skewness andkurtosis values wereexamined, and it was determined that the data were normally distributed. The descriptive statistics of the data included frequency, percentage, mean, standard deviation, minimum, and maximum values. Independent-samples t-test was used to compare sociodemographic data between 2 groups, while comparisons among 3 or more groups were made using one-way analysis of variance (ANOVA). Pearson's correlation tests were used to compare scale scores based on continuous data. Cronbach's alpha analysis was utilized to calculate the reliability of the scale. The level of statistical significance was accepted as $p<0.05$.

Ethical Consideration

All steps of this study complied with publication ethics principles and the principles of the Declaration of Helsinki. Permission was obtained from the directorate of the liver transplantation institute where the study would be conducted with the decision dated 10.05.2022 and numbered E-176197. Approval for the study was obtained from the Non-Interventional Clinical Studies Ethics Committee of Malatya Turgut ÖzalUniversity with the decision dated 26.05.2022 and numbered 2022/9-133. It was ensured that the participants participated in the study by filling out the data collection forms after they read the informed consent form on the first page and agreed to it. The sample included liver transplant patients who voluntarily agreed to participate in the study and filled out the data collection forms.

RESULTS

It was found that 52.3% of the patients who participated in this study were male, 84.7% were married, 31.8% were primary-secondary school graduates, 74.4% were living with their spouses and children, 83.3% received transplants from live donors, 88.6% were following diets, 86.4% had not received education about nutrition, and their mean age was 58.55±7.56 (Table 1).

In the comparisons of the mean ORTO-R scores of the patients based on their sociodemographic characteristics, it was determined that the male patients, the patients who were married, those who had undergraduate or higher degrees, those who were homemakers, those who received their transplants from live donors, those who were not following a diet, and those who had received nutritional education were more orthorexic ($p<0.05$) (Table 1).

Table 1. Distribution of the Mean ORTO-R Scores of the Participants Based on Their Sociodemographic and Nutrition-Related Characteristics

Sociodemographic Characteristics	N	%	ORTO-R Mean Scores ($\bar{x}$± SD)
Sex			
Female	84	47.7	18.25±2.16
Male	92	52.3	16.03±2.72
			t: 5.940, **p: 0.000***
Marital Status			
Married	149	84.7	16.59±2.45
Single	27	15.3	19.81±2.41
			t: -6.280, **p: 0.000***
Education Level			
Literate, no formal degree	23	13.1	15.52±1.62
Primary-secondary school	56	31.8	17.10±2.57
High school	48	27.3	19.35±1.99
Associate degree	25	14.2	16.88±1.39
Undergraduate or higher	24	13.6	14.25±2.36
			F: 27.146, **p: 0.000***
Income Level			
Income < expenses	78	44.3	17.97±2.58
Income ~ expenses	82	46.6	16.67±2.50
Income > expenses	16	9.1	14.09±2.69
			F: 11.438, **p: 0.000***
Occupation			
Civil servant	56	31.8	16.41±2.85
Laborer	23	13.1	17.39±2.62
Freelance	15	8.5	16.93±2.65
Retired	22	12.5	17.90±2.89
Homemaker	25	14.2	15.40±1.25
Not working	35	19.9	18.74±2.14
			F: 6.672 **p: 0.000***
Family Structure			
Living alone	34	19.3	18.79±2.88
Living with parent(s)	11	6.3	17.54±2.58
Living with spouse-children	131	74.4	16.61±2.49
			F: 9.867, **p: 0.000***
Transplant Type			
Cadaveric donor	31	16.7	17.34±2.75
Live donor	155	83.3	15.50±1.61
			t: 4.622, **p: 0.000***
Follows a Diet			
Yes	156	88.6	17.23±2.84
No	20	11.4	15.95±0.22
			t: 5.529, **p: 0.000***
Has Received Education on Nutrition			
Yes	24	13.6	13.54±1.61
No	152	86.4	17.65±2.40
			t: -10.735, **p: 0.000***
	($\bar{x}$± SD)	**Min-Max**	
Age	58.55±7.56	(38-75)	r: -.011, p: 0.883

*p<0.05; t: Independent-Samples t-Test; F: One-way ANOVA; r: Pearson's Correlation Test.

Nutrition-related information was accessed via television by 55.7% of the patients, via the internet by 73.3%, via social media by 69.9%, via scientific publications and articles by 5.7%, via clinic doctors by 63.1%, via clinic nurses by 79.5%, via dieticians by 12.5%, and via family and friends by 75.6% (Table 2). It was found that those who reached information about nutrition through television, internet and social media were moderately orthorexic ($p<0.05$) (Table 2).

Table 2. Distribution of the Mean ORTO-R Scores of the Participants Based on TheirSources of Nutrition-Related Information

Information Sources		N	%	ORTO-RMean Scores ($\bar{x}$± SD)
Television	Yes	98	55.7	16.00±2.72
	No	78	44.3	18.46±2.58
				t: -6.661, **p: 0.000***
Internet	Yes	129	73.3	16.04±2.26
	No	47	26.7	19.95±1.44
				t: -13.0478, **p: 0.000***
Social Media	Yes	123	69.9	16.63±2.65
	No	53	30.1	18.15±2.52
				t: -3.522, **p: 0.001***
Scientific Publication, Article	Yes	10	5.7	18.60±2.79
	No	166	94.3	17.00±2.68
				t: 1.829, p: 0.069
Clinic Doctor	Yes	111	63.1	17.44±2.75
	No	65	36.9	16.49±2.52
				t: 2.273**p: 0.024***
Clinic Nurse	Yes	140	79.5	16.85±2.59
	No	36	20.5	18.02±2.96
				t: -2.360, **p: 0.019***
Dietician	Yes	22	12.5	16.95±3.34
	No	154	87.5	17.11±2.61
				t: -0.210, p: 0.836
Family, Friends	Yes	133	75.6	17.24±2.74
	No	43	24.4	16.60±2.55
				t: 1.359, p: 0.176

*p<0.05, t: Independent-Samples t-Test.

Among the mean ORTO-R item scores of the patients who participated in this study, the highest mean score was 3.46±0.72 in the item "In the last 3 months, did the thought of food worry you?", and the lowest mean score was 1.88±0.93 in the item "Does the thought about food worry you more than three hours a day?" The mean total ORTO-R score of the patient was 17.09±2.70, and their tendency to have orthorexia nervosa was moderate (Table 3).

Table 3. Mean ORTO-RItem and Total Scores of the Participants

ORTO-R Scale Items	Orthorexia	
	Mean	**SD**
1 - In the last 3 months, did the thought of food worry you?	3.46	0.72
2 - Are your eating choices conditioned by your worry about your health status?	2.48	1.10
3 - Does the thought about food worry you for more than three hours a day?	1.88	0.93
4 - Do you think that the conviction to eat only healthy food increases self-esteem?	2.88	0.80
5 - Do you think that eating healthy food changes your lifestyle? (frequency of eating out, friends…)	3.09	0.93
6 - Do you think that consuming healthy food may improve your appearance?	3.27	0.96
Total Orthorexia Mean Score (6-24)	**17.09**	**2.70**

DISCUSSION

ON is a form of an eating disorder that has recently gained attention, and its prevalence is constantly increasing.Today, factors such as the increase in the prevalence of diseases with high mortality and morbidity rates and the lack of sufficient food safety and security in the world have led individuals to pay increased attention to their health (23). This concern results in the association of health-seeking with relevant obsessions, shaping of one's eating habits around strict rules, and development of eating disorders (15). A tendency to display obsessive and hygienic eating behaviors may lead to orthorexia in liver transplant patients. Our study is the first study that investigated the ON tendencies of liver transplant patients receivingimmunosuppressivedrug treatment.

The patients who participated in our study were found to be moderatelyorthorexic (mean score: 17.09±2.70). The male patients were significantly moreorthorexicthan the female patients. In the literature, the rates ON in both sexes have been reported to increase (24-27). In a study that was conducted with performance artists in Turkey,it was emphasized that sex does not have an effect on theorthorexicstatuses of individuals (25). In another study that included 878 medical students, it was found that male students displayed more orthorexictendencies than female students (28). There are different results on sex-based differences in the relevant literature (26,29,30). The results of our study regardingorthorexictendencies were in parallel with the literature. Differences in results may have resulted from the sociocultural characteristics of groups and participants included in different studies.

In our study, the participants who were married had a significantly higher tendency to beorthorexic than those who were single. Arusoğlu et al. also found higher orthorexic tendencies among married individuals (21). In another study, marital status was not found to be effective onorthorexia (20,31). The higher orthorexic tendencies in the married participants

of our study were considered to be associated with the possibility that they could be more obsessed with their health to cope with responsibilities in their family environment.

Among the participants of our study, it was determined that sociodemographic characteristics such as education level, income level, occupation, family structure, and sources of information about nutrition were significantly effective on the ON tendencies of the participants. Highly variable results have been reported in the relevant literature. While Donini reported that ON tendencies decrease as education levels increased, Ernst stated that most individuals who showed ON symptoms were those in the earlier years of their education, those who were single, those without children, and those who were working full-time, but basic demographic characteristics did not have a significant effect on ON (20,30). In their study with 177 participants, Ramacciottiet al. reported the rate of ON as 57.6%, but they emphasized that sociodemographic characteristics were not significantly effective in this result (32). Another study, which was carried out with performance artists, revealed that sex, age, education status, and work experience were not effective on ON (25). In their study in 2014, Varga identified a significant but weak relationship between ON and age, but there was no significant difference between the sexes.Similarly, Bosi et al. did not find a significant effect of sex on individuals' tendencies to have ON (33,34). In the study conducted by Martinovic et al., the mean score of the ORTO-R scale was found to be 13.87±3.06, and this finding was more or less similar to our study (Table 3) (22). It is believed that all these different results have stemmed from differences in the cut-off points of ON scale used by different researchers, differences in populations, and differences in sociocultural settings. Because no study investigating ON tendencies in liver transplant patients, let alone patients with any chronic diseases, was found in the literature review, it was not possible to compare the results of our study to those in similar studies.

Limitations and Strengths of the Study

This study had several limitations. The first was the fact that it was a single-center study, the second was the absence of similar studies in the literature, and the third was the fact that only patients who had undergone organ transplant surgery in the last two years were included. Finally, the number of studies that determined ON using the ORTO-R scale was small. The authors of the revised ORTO-R scale from ORTO-15 state that it should not be used to determine the prevalence of ON. Study data initially collected against the ORTO-15 were recalculated using the ORTO-R scale guidelines.

CONCLUSION

Transplantation surgery is prevalently performed today. One of the important factors that speed up graft survival and the adjustment process after transplantation is balanced nutrition. In our study, it was concluded that the majority of the patients who were using immunosuppressive medication had not received any education on nutrition, and they were moderately orthorexic. It should be kept in mind that this obsessive form of eating will affect balanced nutrition among patients who have gone through a major transplant process.

To not only support advanced-stage liver disease patients in the pre-transplant period but also speed up the adjustment process of these patients to the new organ in the post-transplant period, improve their quality of life and prevent nutrition-related complications, the nutritional statuses of these patients should be assessed as soon as possible, and they should be supported with the appropriate dietary interventions.To make the drug-diet interaction in patients using immunosuppressive drugs after organ transplantation beneficial, ensure that they have a sufficient and balanced diet, and make this diet sustainable, it is important to monitor these patients. Additionally, it is thought that evaluating the pre-transplant orthorexia nervosa tendencies of advanced-stage liver transplant patients will increase post-transplant success, and further studies in this field will be guiding.

Declarations

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Data availability: The data sets obtained in the analysis of this study can be obtained with a request from the responsible author.

Author contributions

NK: Conceptualization, Methodology, Data collection, Writing – Original draft preparation, Control, Supervision. GK: Conceptualization, Methodology, Resources, Writing-Original draft preparation, Formal analysis, Writing-Review and Editing, Control. +00MK: Conceptualization, Control, Data Collection, Data improvement, Writing – Original draft preparation, Writing-Review and Editing, Supervision. We certify that all authors named in this article have read the final version.

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Investigation Of Full Blood Count Parameters, Neutrophil Lymphocyte Ratio And Platelet Lymphocyte Ratio In Patients With Metabolic Syndrome

Metabolik Sendromlu Hastalarda Tam Kan Sayımı Parametreleri, Nötrofil Lenfosit Oranı Ve Trombosit Lenfosit Oranının Araştırılması

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Abstract

Introduction: Metabolic syndrome is a fatal endocrino pathy that starts with insulin resistance and is accompanied by systemic disorders. Neutrophil-lymphocyteratio (NLR) and platelet-lymphocyte ratio (PLR) can be a determinant in inflammation as an alternative to white bloodcell count.

Aim: In this study, metabolic syndrome characterized by endothelial dys function, subclinical inflammation and hypercoagulability and systemic inflammation indicator; It is aimed to show there lationship between neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR).

Method: The study was carried out by retrospectively examining the demographic information and laboratory records of the patients who applied to Gaziantep Private Emek Hospital Internal Medicine Polyclinic between 01/10/2022-30/12/2022 for general health controlor Type 2 DM follow-up. The cases were divided into 2 groups as metabolic syndrome and control group. 63 patients with metabolic syndrome and 53 healthy (control group) patients were included in thestudy.

Results: The neutrophil-lymphocyte ratio (NLR) was 3.44 (2.87-4.1) in the metabolic syndrome group (n=63), and the NLR was 1.81 (1.65-2.04) in the control group (n=53), and there was a statistically significant difference ($p<0.001$). The platelet-lymphocyte ratio (PLR) was 198 (169.5-228.5) in the metabolic syndrome group and 101 (87.7-114.2) in the control group and was statistically significant ($p<0.001$).

Conclusion: Metabolic syndrome, which is the cause of low-grade chronic inflammation, and NLR and PLR levels, which are easily and in expensively accessible indicators of inflammation, were compared, and NLR and PLR levels were found to be significantly higher in the metabolic syndrome group. This result shows us that these two inflammation parameters can be used as prognostic indicators in chronic diseases.

Keywords: Metabolic Syndrome, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio.

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Özet

Giriş: Metaboliksendrom insülin direnci ile başlayan ve sistemik bozuklukların eşlik ettiği ölümcül bir endokrinopatidir. Nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR), lökosit sayısına alternatif olarak inflamasyonda belirleyici olabilir.
Amaç: Bu çalışmada endoteldisfonksiyonu,subklinikinflamasyon, pıhtılaşma artışı ve sistemik inflamasyon göstergesi ile karakterize metaboliksendrom; nötrofil-lenfosit oranı (NLR) ile trombosit-lenfosit oranı (PLR) arasındaki ilişkinin gösterilmesi amaçlanmaktadır.
Yöntem: Çalışma, Gaziantep Özel Emek Hastanesi Dahiliye Polikliniğine 01/10/2022 - 30/12/2022 tarihleri arasında genel sağlık kontrolü veya Tip 2 DM takibi için başvuran hastaların demografik bilgileri ve laboratuvar kayıtları retrospektif olarak incelenerek yapılmıştır. Olgular metaboliksendrom ve kontrol grubu olarak 2 gruba ayrıldı. Çalışmaya 63 metabolik sendromlu hasta ve 53 sağlıklı (kontrol grubu) hasta dahil edildi.
Bulgular: Metaboliksendrom grubunda (n=63) nötrofil-lenfosit oranı (NLO) 3,44 (2,87-4,1), kontrol grubunda (n=53) NLO 1,81 (1,65-2,04) ve istatistiksel olarak anlamlı bir farktı ($p<0.001$). Trombosit-lenfosit oranı (PLR) metaboliksendrom grubunda 198 (169,5-228,5), kontrol grubunda 101 (87,7-114,2) olup istatistiksel olarak anlamlıydı ($p<0,001$).
Sonuç: Düşük dereceli kronik inflamasyonun nedeni olan metaboliksendrom ile inflamasyonun kolay ve ucuz ulaşılabilir göstergeleri olan NLR ve PLR düzeyleri karşılaştırılmış ve metabolik sendromda NLR ve PLR düzeylerinin anlamlı olarak yüksek olduğu saptanmıştır. Bu sonuç bize bu iki inflamasyon parametresinin kronik hastalıklarda prognostik göstergeler olarak kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Metabolik Sendrom, Nötrofil Lenfosit Oranı, Platelet Lenfosit Oranı.

INTRODUCTION

Metabolic syndrome (MetS) is a complex of diseases characterized by decreased insulin sensitivity as the main pathology and root cause, weight gain, onset of diabetes, high cholesterol, high blood pressure, and accumulation of oxidized low-density lipoprotein (LDL-Cholesterol) in the heart vessels. The formation of foam cells by macrophages is the most important step in the formation of oxidized LDL. These foam cells accumulate in the subendothelial tissue and form fatal prothrombotic lesions. Since it is the disease of our modern age, it would be correct to call it the disease of civilization complex. It attracted attention for the first time in the 1980s, and scientists had problems in naming it due to the coexistence of all metabolic diseases affecting the cardiovascular bed, and it was called unidentified (X) disease. Obesity, subclinical inflammation, and insulin resistance are features that define the MetS (1).

One of the mechanisms involved in the pathogenesis of metabolic syndrome is a chronic inflammatory process. In abdominal obesity, prothrombotic and inflammatory responses are triggered by fatty tissue-derived metabolic products, hormones and cytokines. Leukocytosis is the hemogram value that best shows acute and chronic inflammation in the body. NLR and PLR can be a determinant in inflammation as an alternative to white blood cell count. NLR may be elevated due to the potential conditions that create atheroma plaque in the entire vascular bed of the body, such as diabetes, hypertension, sedentary lifestyle, western diet, carbohydrate-heavy diet, family history of cardiovascular disease and metabolic diseases. It is an indicator of inflammation that can show the course of cardiovascular diseases and predict the risk of death. NLR is a value that is directly affected by the increase in other inflammatory indicators such as procalcitonin, C-Reactive Protein (CRP), and systemic inflammation index (SII) (2).

Both NLR and PLR, as well as CRP and procalcitonin levels were found to be high in patients with bipolar disease, mania, depression and panic attacks. In addition, these markers increased in the age group of children with attention deficit.We know that the reason for subclinical chronic inflammation in all these mood disorders is the intake of foods high in sugar and

carbohydrates, and the leaching of pesticides into the soil, vegetables and fruits. We call these foods and ingredients inflammatory foods (3). In patients with metabolic syndrome, glycated low-density lipoprotein (GLDL-C) is directly related to platelet count and PLR (4).

The inflammatory indices NLR, PLR and SII are complete blood count rates and diseases that have predictive importance in MetS and oncological diseases (5).

In this study, metabolic syndrome characterized by endothelial dysfunction, subclinical inflammation and hypercoagulability and systemic inflammation indicator; It is aimed to show the relationship between NLR and PLR.

METHOD

The study was carried out by retrospectively examining the demographic information and laboratory records of patients who applied to Gaziantep Private Emek Hospital Internal Medicine Polyclinic between 01/10/2022 and 30/12/2022 for general health check-up or Type 2 diabetes mellitus (DM) follow-up. First of all, blood pressure measurement and waist circumference measurements were recorded in terms of National Cholesterol Education Program/Adult Treatment Panel (NCEP-ATP III) criteria of the patients who applied to the outpatient clinic, and they were evaluated for the presence of MetS (6) (Table 1).

Table 1. NCEP-ATP III Diagnostic Criteria For Metabolic Syndrome.

Parameter	Criteria
Abdominal obesity	Waist circumference ≥102 cm in male and ≥88 cm in female
Triglyceride (TG)	≥ 150 mg/dl
HDL-cholesterol	<50 mg/dl in female and <40 mg/dl in male, or take medication for it
Blood pressure	≥130/85 mmHg
Fasting blood glucose	≥100 mg/dl

The cases were divided into 2 groups as MetS and control group. The control group consisted of individuals with normal body mass index (BMI), no hypertension, diabetes, insulin resistance and known chronic disease, HbA1c < 5.7% and no drug prescribed for the last 6 months. Those with hemoglobinopathy, anemia were not included in the study. In total, 63 patients with metabolic syndrome, 53 healthy; 116 patients with available biochemical data were included in the study. Complete blood count parameters, NLR and PLR of both groups were compared. Body mass indexes of the patients were calculated using the formula BMI = kg/m². Age, gender, weight and height values and waist circumference of the patients were recorded and fasting blood glucose, Hba1c, lipid profile, hemogram, sedimentation and CRP levels were examined in both groups (blood taken after 8-12 hours of fasting).

The IBM Statistical Package for the Social Sciences (SPSS) version 25 was used for the statistical analysis of our study. The Kolmogorov-Smirnov test was used to determine whether the values we obtained were suitable for normal distribution. While defining the results, standard deviation and mean for those with normal distribution, and median and quartile range (IQR) forms for the others were used. The group comparison of the values with normal distribution was made with Student-T, while the Mann Whitney U test was used in the others. If the P value was below 0.05, the result was said to be significant.

RESULTS

The gender distribution ratios of the 116 participants included in the study are shown in Table 2. The mean age was 42±12 years in the MetS group and 43.6±11.76 years in the control

group. Since the cases were selected from similar age groups, there was no difference between the mean ages (p=0.45).

Table 2. Age And Gender Distribution By Groups

Group Name	MetS group	Control group
Average age	42±12	43,6±11,76
Gender distribution (Female/Male)	33/30	28/25
Total count of patients	63	53

When the NLR of the groups are examined; The NLR was 3.44(2.87-4.1) in the MetS group and 1.81 (1.65-2.04) in the control group (p<0.001).When we have a detailed look at thePLR values of the groups; PLR was 198 (169.5-228.5) in the MetS group and PLR 101 (87.7-114.2) in the control group (p<0.001). Absolute neutrophil count was 5.77±0.75 (10^3mm^3) in the MetS group and 3.89±0.79 (10^3mm^3) in the control group, (p<0.001). Absolute lymphocyte count was 1.69±0.29 (10^3mm^3) in the MetS group and 2.09±0.31 (10^3mm^3) in the control group (p<0.001). The platelet count was 340 (299-381) (10^3mm^3) in the MetS group and 210 (189-238) (10^3mm^3) in the control group (p<0.001). The CRP level in the MetS group was 4.1 (3.9-4.6) mg/dL, and the CRP level in the control group was 1.6 (1.07-1.8) mg/dL (p <0.001). The sedimentation level in the MetS group was 17 (15-19) (1st hour), and the sedimentation level in the control group was 7 (5-10) (1st hour) (p<0.001).

FBG level 168 (146.5-195.8) mg/dL and HbA1c level 7.8% (7.1-8.6) in the MetS group, FBG level 89 (85-93) mg/dL and HbA1c level % in the control group; It was found to be 5.3 (5-5.5) (p<0.001 for each 2 values).

When the blood pressure levels of the groups were compared, the systolic blood pressure level was 136 (126-143) mmHg and the diastolic blood pressure level was 85 (77-92) mmHg in the MetS group, the systolic blood pressure level was 111 (108-118) mmHg and the diastolic blood pressure level was 65(58-70) mmHg in the control group (p<0.001 for both values).

Table 3. Comparison Of Metabolic Syndrome And Control Group In Terms Of Study Parameters

Group Name	MetS group (n=63)	Control group (n=53)	p
FBG (mg/dL)	168 (146,5-195,8)	89 (85-93)	<0,001
HbA1c (%)	7,8 (7,1-8,6)	5,3 (5-5,5)	<0,001
BMI(kg/m^2)	33,3 (31,9-34,6)	23,2 (22,5-23,7)	<0,001
Waist circumference (cm)	103,3 (94,1-110,4)	79,2 (77,2-86,4)	<0,001
Waist circumference-female (cm)	94,3 (91,5-98,8)	77,4 (75,3-78,2)	<0,001
Waist circumference-male (cm)	111,5±8,5	86,6±2,09	<0,001
Systolic blood pressure (mmHg)	136 (126-143)	111 (108-118)	<0,001
Diastolic blood pressure(mmHg)	85 (77-92)	65 (58-70)	<0,001
Triglyceride (mg/dL)	250±50,8	121±14,5	<0,001
HDL-Cholesterol(mg/dL)	40±5,79	65±4,85	<0,001
HDL-Cholesterol-female(mg/dL)	42,5±5,4	66,6±4,8	<0,001
HDL-Cholesterol-male(mg/dL)	37±4,82	62,5±3,93	<0,001
CRP (mg/dL)	4,1 (3,9-4,6)	1,6 (1,07-1,8)	<0,001
Sedimentation (1st hour)	17 (15-19)	7 (5-10)	<0,001
Neutrophil (absolute) count (10^3mm^3)	5,77±0,75	3,89±0,79	<0,001
Platelet count (10^3mm^3)	340 (299-381)	210 (189-238)	<0,001
Lymphocyte (absolute) count (10^3mm^3)	1,69±0,29	2,09±0,31	<0,001
Neutrophil-Lymphocyte ratio (NLR)	3,44 (2,87-4,1)	1,81 (1,65-2,04)	<0,001
Platelet-Lymphocyte ratio (PLR)	198 (169,5-228,5)	101 (87,7-114,2)	<0,001

When the lipid profiles of the groups were compared, the triglyceride level was 250±50.8 mg/dL and HDL-cholesterol level was 40±5.79 mg/dL in the MetS group, while the triglyceride level was 121±14.5 mg/dL and HDL-cholesterol level was 65±4.85 mg/dL in the control group ($p<0.001$ for both values).

When the waist circumference and body mass index (BMI) of the groups were compared, the waist circumference in the MetS group was 103.3 (94.1-10.4) cm and the BMI was 33.3 (31.9-34.6) kg/m². In the control group, waist circumference was 79.2 (77.2-86.4) cm and BMI was 23.2 (22.5-23.7) kg/m² ($p<0.001$ for both values) (Table 3).

DISCUSSION

MetS is a group of combined diseases that give signs and symptoms with high blood sugar, decrease in insulin sensitivity, increase in body fat mass, high blood pressure, high cholesterol, apple-type adiposity in which the lower extremities are thin and the body is thick, and eventually progress to cardiovascular diseases. It also includes endothelial dysfunction, prooxidant, prothrombotic and inflammatory processes. With the formation of low-grade subclinical systemic inflammation, increase in inflammatory parameters, oxidation, that is, premature aging, continues with damage to the vascular bed that feeds the vital organs (7, 8).

NLR is a commonly used test, even in Grade 1 healthcare facilities. NLR is thought to be an indicator of subclinical inflammation (9). Studies have shown that there is a subclinical inflammation in diseases such as diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome, endothelial dysfunction and NLR is an indicator of this inflammation (10). As inflammatory markers, NLR and PLR are frequently preferred in studies conducted in different clinical pathologies and patient groups. Conditions such as malignancy, neurodegeneration, acute systemic infection, smoking addiction can be included in these study groups (11).

These two inflammatory parameters have been used to determine the course of cardiovascular system diseases, high blood sugar and malignancies (12). NLR is used to determine the general condition and course of the patient after treatment of malignant disease and MetS. It can also determine whether metabolic syndrome will develop in a healthy individual in the future (13). It is known that NLR and high sensitivity CRP (hs-CRP) levels are higher in patients with metabolic syndrome than in normal individuals (14). MetS is associated with chronic inflammation, high CRP, sedimentation, leukocytes and NLR (15).

In our study, confirming this, the NLR value in the MetS group [3.44 (2.87-4.1)] was detected to be higher than the control group [1.81 (1.65-2.04)] ($p<0.001$). Likewise, CRP level [4.1 (3.9-4.6)] mg/dL in the MetS group was detected to be increased in the other group[1.6 (1.07-1.8)] mg/dL ($p<0.001$). When the leukocyte counts were examined, in accordance with the literature, the leukocyte count in the MetSgroup (7.78±0.78) 10^3mm^3 was detectedto be increased in the other group(6.43±0.85) 10^3mm^3 ($p<0.001$). When the sedimentation levels were examined, it was found that it was 17 (15-19) (1st hour) in the MetS group and 7 (5-10) (1st hour) in the control group ($p<0.001$).

In a study, it was determined that both platelet and PLR did not increase in patients with MetS(16). In our study, the platelet count [340 (299-381)] was higher in the metabolic syndrome group compared to the control group [210 (189-238)] ($p<0.001$). In addition, PLR [198 (169.5-228.5)] was found to be higher in the metabolic syndrome group compared to the control group [101 (87.7-114.2)] ($p<0.001$).

In a study by Varol et al., NLR showed a negative correlation with high-density lipoprotein (HDL), which has anti-inflammatory activity. Patients with low HDL-cholesterol had significantly higher NLR compared with control participants (17). In our study, HDL-cholesterol level with anti-inflammatory effect was 40±5.79 mg/dl in the metabolic syndrome group and 65±4.85 mg/dl in the control group ($p<0.001$).

The lymphocyte/HDL ratio was found to be increased in metabolic syndrome and is an effective predictor of metabolic syndrome. Again in the same study, it was observed that the platelet-lymphocyte ratio did not increase (18). In our study, in accordance with this literature, the lymphocyte/HDL-Cholesterol ratio [0.041 (0.035-0.052)] in the MetS group was detected to be 0.0233 increased in the other group (0.03-0.035) in the in the other group($p<0.001$).

Inflammation is closely associated with insulin resistance due to excess adipose tissue that produces proinflammatoryadipokines that result in low-grade chronic inflammation, impair the tissue response to insulin, and lead to type 2 diabetes. HbA1c levels >7% are associated with a higher risk of irreversible, organic injury, but HbA1c certainly does not predict inflammatory processes (19,20). In our study, HbA1c level [7.8% (7.1-8.6)] in the metabolic syndrome group was found to be higher than >7% and higher and statistically significant compared to the control group [5.3% (5-5.5)]. ($p<0.001$).

In the study of Atak et al., the platelet-lymphocyte ratio can be used to detect low-grade inflammation caused by diabetes. It was determined that PLR was increased in cases with high sugar levels for many years compared to normal individuals. It has been found that PLR and 3-month sugar indicator are directly related to each other in cases with high blood sugar. The PLR value is an indicator of the course of the disease in diabetics and whether it harms other organs. As the sugar level rises as a result of the diabetic's weakness in the use of medication and not paying attention to his diet, PLR and similar indicators increase with the sugar level (21). In our study, direct relationshipwas detected between HbA1c and PLR in accordance with this literature ($p=0.03$).

PLR, and especially NLR, has been associated with microvascular and macrovascular complications in diabetes, most notably with disease progression and metabolic deterioration. In a study by Sefil et al., it showed a positive correlation with NLR and HbA1c levels. This study showed a difference in the proportions of hyperglycemic subjects with HbA1c <7.0% and hyperglycemic subjects with HbA1c ≥7.0% (22). In our study, a positive correlation was found with NLR and HbA1c levels in accordance with this literature ($p=0.02$).

Obesity has become a growing problem around the world and is turning into a pandemic. It is a component of the complex of metabolic diseases. Obesity is a precursor disease for vascular bed diseases, osteoporosis, uterine and breast malignancies. If obesity is treated, all the conditions it causes are also treated. Ratios such as NLR, PLR and SII obtained from complete blood count (CBC) and its results have been associated with obesity and obesity-related diseases (23). In our study, the BMI level was 33.3 (31.9-34.6) kg/m² in the obese group with metabolic syndrome and 23.2 (22.5-23.7) kg/m² in the control group ($p<0.001$). In our study, NLR and PLR were found to be higher and statistically significant in the obese group with metabolic syndrome compared to the control group in accordance with the literature ($p<0.001$ for both values).

In many studies, leukocyte count has been found to be an independent risk indicator for diabetes, insulin resistance, metabolic syndrome, obesity and coronary artery diseases (24). In human and animal experiments, it has been determined that increased leukocyte and neutrophil counts are associated with obesity and metabolic disorders triggered by obesity

(25). An increased leukocyte count is a direct risk factor for the development of MetS (26). When the leukocyte counts were examined in our study, the leukocyte count in the MetSgroup (7.78±0.78) was found to be higher than 10^3mm^3 and the control group (6.43±0.85) 10^3mm^3, in accordance with the literature ($p<0.001$).

In a study by Furuncuoğlu et al., it was determined that there was no statistically significant relationship between the degree of obesity and PLR and NLR. However, white blood cells, neutrophils, lymphocytes, platelets, and plateletcrit (PCT) levels were statistically significantly affected by the increase in body mass index (27). In some previous studies, it was observed that neutrophil and lymphocyte counts increased in patients with obesity and MetS compared to control groups, and NLR increased, but this was not very significant (28). In our study, the plateletcrit (PCT) level in the MetS group was 0.31±0.03%, 0.20±0.02% in the control group ($p<0.001$).

Mean platelet volume (MPV) indicates the mean volume and functionality of platelets. It can be used as an inflammatory marker such as NLR and PLR. There are close links between MPV, metabolic syndrome and cardiometabolic risk. The incidence of MetS in women was higher in the low MPV group than in the high MPV groups (29). In our study, the MPV level was found to be 11.3±0.68 fL in the MetS group and 8.7±0.59 fL in the control group ($p<0.001$).

CONCLUSION

In conclusion, in our study, the relationship between metabolic syndrome and inflammation markers NLR, PLR, CRP and sedimentation was investigated and inflammatory markers were detected to be increased in the group with metabolic syndrome. It is thought that NLR and PLR can be used as simple, effective and low-cost hematological tests in the follow-up of MetS and its components and in determining the burden of disease. Large-scale and multicenter studies in mass of peopleare needed for the use of NLR and PLR in follow-up and prognosis in metabolic syndrome.

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The Effects of Esports Experience on Hand Function, Strength, Coordination and Pain in Elite League of Legend Players

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Abstract

Introduction: Esports, also called electronic sports, refers to organized multiplayer video game competitions where players or teams compete against each other. With the increasing popularity of e-sports, the fact that these sports involve sitting for long periods of time indicates that they can cause physical problems and may occur in that region as they frequently used the hand region.
Objective: This study aims to assess the relationship between e-sports experience and hand function, strength, coordination and pain in professional e-sports athletes.
Method: Twenty professional esports players (mean age; 18.50±1.90 years) participated voluntarily. Hand grip strength with a Jamar hand dynamometer, hand function disability and symptoms with the Disability of Arm Shoulder and Hand Questionnaire (DASH) and Participants' pain levels with the Visual Analog Scale, hand coordination with The Purdue Pegboard Test were measured.
Results: The results revealed a significant moderate correlation ($r=0.443$; $p<0.05$) between the duration of e-sports experience and DASH scores, indicating potential hand function issues. Furthermore, a significant difference in DASH scores was observed based on the duration of e-sports experience ($t=-2.203$, $p=0.041$). Additionally, A positive, statistically significant relationship was demonstrated between daily e-sports time in hours and VAS ($r=0.472$; $p=0.035$). There was a statistically significant difference regarding dominant hand measurement according to e-sports experience years between the groups ($t=-2.101$; $p=0.049$).
Conclusion: These insights are of great importance for a deeper understanding of hand related parameters in e-sports athletes and contribute to the development of effective strategies and interventions for injury prevention and health promotion in this field.

Keywords: Esports, Gaming, Hand, Pain, Coordination, Function.

INTRODUCTION

Esports, also called electronic sports (e-sports) or competitive gaming, refers to organized multiplayer video game competitions where players or teams compete against each other. The popularity of e-sports has rised over the nearly 70-year history of computer gaming. Referred to as e-sports, this new form of professional gaming has emerged as a crucial and immensely popular aspect of video game communities, especially among adolescents and emerging adults. Over the years, the prize money in esports has undergone a remarkable surge, reaching unprecedented heights. Additionally, the number and scale of events have consistently expanded yearly, catering to the growing demand from players and fans alike. Furthermore,

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the emergence of e-sports betting has added another dimension to the industry, allowing enthusiasts to engage with their favorite teams and players in a new and exciting way (1-4).

E-sports is characterized by many individuals dedicating long hours to playing computer games. Similar to watching TV, using a computer or smartphone, playing video games is a sedentary activity that involves prolonged periods of inactivity and sitting. These sedentary habits are known to increase the risk of non-communicable diseases and overall mortality (5-9).

Playing video games, in addition to a seated position, demands precise motor skills. Immersion in virtual environments necessitates repetitive movements of the arms, wrists, hands, and fingers, making it comparable to certain forms of office work or even more physically demanding activities. With regards to computer usage, studies have explored the relationship between mouse usage and musculoskeletal symptoms, revealing that mouse use can contribute to discomfort in the neck and wrist, particularly due to arm posture. The risk factors for forearm pain in computer-related jobs, specifically mouse usage, have been highlighted as well (10). Extended computer usage and prolonged sitting have been found to significantly impact the upper extremities, resulting in various musculoskeletal problems. Physiotherapists often encounter issues related to the neck, shoulders, and back, mainly due to the seated position and the choice of chair or table, which can strain the stabilizing muscles, leading to occasional pain (11). Repetitive strain injuries, caused by the impact of fingers on the mouse or keyboard, can also occur, especially if users do not have specialized gaming accessories. Wrist compression can lead to conditions such as carpal tunnel syndrome, resulting in various hand problems. Additionally, a sedentary lifestyle associated with screen-based activities, including playing video games, can contribute to muscle problems like tendon shortening, strength loss, fatigue, and other issues throughout the body, such as circulatory problems, obesity, and more (10,12).

A study conducted by Lindberg et al. (13), provides compelling insights into the prevalence and implications of musculoskeletal (MSK) pain in e-sports athletes. This com-prehensive study comprised 188 Danish e-sports athletes aged between 15-35 years and revealed that an alarming 42.6% of the participants reported experiencing MSK pain in the previous week. A key finding was that the most prevalent site of this pain was the back, with a substantial 31.3% of athletes reporting back pain. Moreover, a noteworthy correlation was identified between MSK pain and the volume of e-sports-related training. Intri-guingly, the athletes experiencing MSK pain participated significantly less in e-sports training compared to those who were pain-free. According to a study by Fathuldeen et al. (14), with 116 participants, 86.2% (approx-imately 100 individuals) reported at least one gaming-related musculoskeletal injury. The areas most affected were the lower back (63.8%, equivalent to roughly 74 individuals), neck (50%, about 58 individuals), hand/wrist (44.8%, approximately, 52 subjects), and shoulder (35.3%, 41 subjects).

According to a systematic review, excessive video gaming durations, particularly those exceeding 3 hours per day, have been identified as a predictor for the onset of musculoskeletal disorders. The most reported symptoms of these disorders include neck, shoulder, and back pain. The study further underscores that as video gaming duration increases, so does the likelihood of musculoskeletal disorders, with odds ratios (ORs) significantly increasing between 1.3 to 5.2 in eight out of ten studies that reported ORs. These findings highlight the need for the development of targeted and tailored prevention and health promotion programs specifically for e-sports athletes and gamers in general. This is a crucial public health matter that brings attention to the potential conse-quences of the sedentary lifestyle and repetitive

movements engendered by video gaming (10). Furthermore; a study Ekefjärd et al. (15), conducted a cross-sectional study to determine the prevalence of self-reported musculoskeletal pain among professional gamers, as well as its potential correlation with various lifestyle factors. Out of the 40 professional gamers who responded to their electronic survey, a significant 62.5% (25 subjects) reported experiencing at least one physical symptom in the three months leading up to the survey. The study discovered a notable correlation between the amount of time spent gaming and the reported physical symptoms. More specifically, those who played more than 35 hours per week were eight times more likely to report physical symptoms (OR=8.0; 95% CI 1.4-44.6, p=0.018).

The emergence of e-sports as a prominent form of athletic competition has brought about new challenges in managing the health of e-sports athletes. Despite the increasing popularity of e-sports, the physical ailments experienced by these athletes, often attributed to prolonged sedentary behavior, have been underreported and potentially overlooked (16). Research indicates a high prevalence of musculoskeletal complaints among elite League of Legends players, particularly in relation to hand function, strength, coordination and pain. These findings highlight the need for further investigation into the effects of e-sports experience on the physical well-being of players in order to develop appropriate interventions and support systems to ensure their long-term health and performance (17).

To the best of our knowledge, no previous studies have examined the relationship between e-sports experience and hand function, strength, pain and coordination. Therefore, the primary objective of this study is to investigate the effects of e-sports experience on hand function, strength, coordination and pain among elite League of Legends players. Additionally, this study aims to compare the effects of e-sports experience on hand function, strength, coordination and pain. By specifically focusing on the impact on hand functionality, muscular strength and coordination as well as the presence of pain, this research aims to enhance our understanding of the physiological demands and potential risks associated with participating in competitive e-sports. The findings of this study will provide valuable insights for player health management and contribute to the development of targeted interventions aimed at optimizing performance and minimizing potential adverse effects.

METHOD

Study Design

The present cross-sectional study was conducted at the Sportscare Clinic among elite male e-sports athletes. Before the study, all participants were informed about the study and read and signed the informed consent form. The data collected at the end of the study were analyzed with G*Power 3.0.10 program and power analysis was made. The power of the study was determined as 80% for a sample of 20 people with a 5% margin of error and a defined effect size. Firstly, twenty Elite League of Leg-ends athletes were included to the study according to inclusion criteria. Then, the clinical evaluations are performed. All e-sports athletes were evaluated in terms of hand disability, function, strength and pain by same physiotherapists. The study was approved by the decision of the Interventional Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (protocol number: 158).

Participants

The study included 20 elite male e-sports athletes who play League of Legends in Istanbul. Inclusion criteria were determined as being an e-sports player for at least one year, aged between 18 and 25, and belonging to the group of professional e-sports athletes. Players were

excluded from the study if they had had a history of systemic diseases, surgery related to hand fractures or injuries, or recent receipt of local steroid injection or physiotherapy within the past six months and the presence tumor.

Assessment Procedures

After informed consent, a structured questionnaire was filled out through face-to-face to collect their socio-demographic conditions (age, gender, body mass index, presence of chronic diseases, hand dominance and training habits). Additonally, 20 professional male e-sports athletes were questioned in terms of previous injuries and surgery they had experienced in the last 6 months initially. All athletes were evaluated in terms of hand disability, function, strength, and pain. All measurements were made by determining the rest times when e-sports players were not involved in training or competition. The same physiotherapist carried out the evaluations at the same time intervals in a quiet room, closed to external stimuli, with suitable lighting and ventilation. Before assessment, athletes were rested for 2 hours.

Upper Extremity Disability Evaluation

Hand function was assessed using The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a reliable and validated instrument. This questionnaire evaluates all upper extremity functions and consists of a total of thirty questions. 21 of the questions of the questionnaire question the ability to perform functional activities, 5 of them about pain and 4 of them about the psychosocial effects of the disease. Each question is scored using a 5-point Likert scale with a range of 1-5. The total score of the questionnaire varies between 0-100 points, higher scores indicate better functional status (18,19).

Pain Assessment

Hand pain was assessed using a Visual Analogue Scale (VAS) a widely recognized tool for pain assessment. The athletes were asked to mark their current level of pain on the VAS, providing a visual measure of their pain experience. Participants were asked to indicate pain severity they felt on a 10 cm horizontal line, ranging from 0 to 10. Zero shows no pain and 0 is intolerable pain. Pain intensity was recorded by measuring the value of the marked place in cm. Higher values indicate more severe pain (20,21).

Strength Measurements

Handgrip strength was evaluated using a Jamar Hand Dynamometer, which is a standardized and validated tool. For each of the tests of hand strength, the subjects were seated with their shoulder adducted and neutrally rotated, elbow flexed at 90°, forearm in a neutral position and wrist between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation. The testing protocols consisted of two maximal isometric contractions for 5 s, alternating from left to right with a 1-minute rest between measurements and the highest value was used for determination of maximal grip strength. The process was repeated on the dominant and non-dominant sides, and the averages were recorded in kg (22).

Manual dexterity and Coordination Assessment

The Purdue Pegboard Test was used to assess hand coordination and manual dexterity. The test has five more subtests. While one of them involves mathematical addition, in the other tests the athletes do the tasks actively. While scoring the test, the pins, washers and nuts inserted in the given time were counted. For this evaluation, three different measurements were taken from the athletes and the highest value of measurements was recorded (23).

Statistical Analysis

The data were analyzed using SPSS version 27.0 Significance was set at 0.05 ($p \leq 0.05$) a priori. The Kolmogorov–Smirnov test was used to test the normality of data distribution. While descriptive statistics for normally distributed numerical variables are given with mean and standard deviation. Parametric methods were used for measurement values suitable for normal distribution. Parametric methods, including the Independent Sample T-Test, were used for measurement values suitable for normal distribution while non-parametric methods, the Mann-Whitney U-Test method was used for the measurement values that did not conform to the normal distribution. Additionally, relationships between variables were calculated with Pearson correlation test in normally distributed data. In cases where at least one quantitative variable did not show a normal distribution, the "Spearman" correlation coefficient was used.

RESULTS

Bu bölüm Times New Roman ve 12 punto ile yazılmalıdır. Her başlıktan ve paragraftan sonra alt boşluk eklenerek yeni paragrafa geçilmelidir.The data on the physical characteristics of the athletes included in the study are shown in Table 1. According to the table, it was observed that the mean age of the participants was 20.85±2.32 (years). It was found that participants 55.0% were above 21 years and 70.0% had the right-hand dominant. Also, Table 1 showed that 60.0% (n=12) of participants were overweight. 60.0% of all athletes included in the study had e-sports experience of above 4 years, 55.0% (n=11) had a daily e-sport activity time of above 9 hours, and all athletes do not participate in any sports activity. Table 1 also indicated that 50.0% of all athletes slept below 7 hours daily (Table 1).

Table 1. Characteristics of Esports Players

Variable (N=20)	n	%
Age [$\bar{X} \pm SD \rightarrow 20.85 \pm 2.32$ (years)]		
≤20	9	45.0
≥21	11	55.0
Gender		
Male	20	100.0
Dominant hand		
Right	14	70.0
Left	6	30.0
BMI [$\bar{X} \pm SD \rightarrow 20.85 \pm 2.32$ (kg/m^2)]		
Normal (18.5 kg/m^2 ≤ BMI ≤24.9 kg/m^2)	8	40.0
Overweight (25.0 kg/m^2 ≤ BMI ≤29.9 kg/m^2)	12	60.0
E-sports experience [$\bar{X} \pm SD \rightarrow 3.80 \pm 1.32$ (years)]		
≤3 year	8	40.0
≥4 year	12	60.0
Daily E-sports time [$\bar{X} \pm SD \rightarrow 8.63 \pm 1.46$ (hours)]		
≤8 hour	9	45.0
≥9 hour	11	55.0
Physical activity		
No	20	100.0
Daily sleep time [$\bar{X} \pm SD \rightarrow 7.80 \pm 1.56$ (hours)]		
≤7 saat	10	50.0
≥8 saat	10	50.0

Data expressed as mean ± standard deviation and percentages (**%**), SD: Standard deviation. n: number of participants, BMI: Body mass index.

As shown in Table 2, a statistically significant difference was found in terms of DASH scores according to e-sports experience duration classes (t=-2.203; p=0.041). E-sports players with four and more than four years of sports experience had worse scores in terms of disability compared to those with three and less than three years of sports experience. However, Table 2 also revealed that there was no statistically significant difference in Purdue Pegboard measurement values according to e-sports experience (p>0.05). It was determined that the e-sports experience duration was similar regarding the specified features. Moreover, as seen in Table 2, there was a statistically significant difference regarding dominant hand measurement according to e-sports experience between groups while (t=-2.101; p=0.049). It was found that those with four and more than four years of e-sports experience had significantly higher dominant hand strength than those with three and less than three years of experience. Contrarily, there is no statistically significant difference in terms of VAS scores according to e-sports experience between groups. (p>0.05, Table 2).

Table 2. Comparison of Hand Disability, Function, Strength And Pain Scores By Esports Experience İn Years

Sports Experience	≤3 years (n=8)		≥4 years (n=12)		t/z value P value
Variable (N=20)	$\bar{X} \pm SD$	**Median**	$\bar{X} \pm SD$	**Median**	
DASH score	2.01±1.65	2.5	3.85±2.09	3.8	t=-2.203 **p=0.041**
Purdue Pegboard score	29.38±4.66	29.0	27.58±3.06	26.0	Z=-0.794 p=0.427
VAS score	2.75±0.71	3.0	3.50±1.00	3.5	t=-1.831 p=0.084
Dominant hand grip strength (kg)	38.50±2.84	39.0	40.58±1.61	41.3	t=-2.101 **p=0.049**
Non- dominant hand grip strength (kg)	36.94±2.31	36.8	38.88±3.06	39.0	Z=-1.129 p=0.256

Data expressed as mean ± standard deviation and median. "Independent Sample-t" test was used to compare the measurement values for normal distribution. Mann-Whitney U" test was used for it did not conform to the normal distribution. VAS: Visual Analogue Scale, DASH: Disabilities of the Arm, Shoulder and Hand.

A positive, weak, and statistically significant relationship was found between e-sports experience in years and DASH (r=0.443; p=0.049). Also, there was a positive, moderate, and statistically significant relationship between e-sports experience in years and VAS (r=0.591; p=0.006). As e-sports experience years increase, VAS score will increase. A positive, weak, and statistically significant relationship was demonstrated between daily e-sports time in hours and VAS (r=0.472; p=0.035, Table 3).

Table 3. Relationships Between E-Sports Experience İn Years And Daily E-Sports Duration İn Hours Measurement Values

Correlation* (N=20)	E-sports experience (years)		Daily E-sports time (hours)	
	r	*p*	*r*	*p*
DASH score	0.443	**0.049**	0.423	0.063
Purdue Pegboard score	-0,197	0.406	0,283	0,241
Dominant hand strength	0.186	0.490	0.086	0.544
Non- dominant hand strength	0,122	0,637	-0,156	0,516
VAS score	0.591	**0.006**	0.472	**0.035**

*Pearson correlation coefficient was determined when examining the relationships of two quantitative variables with normal distribution. In cases where at least one quantitative variable did not show a normal distribution, the "Spearman" correlation coefficient was used. DASH: Disabilities of the Arm, Shoulder and Hand, VAS: Visual Analogue Scale.

DISCUSSION

The current study aimed to examine the association between e-sports experience and hand function, disability, strength, and pain. The findings of the study revealed some interesting insights into the literature. Specifically, individuals with four or more years of e-sports experience exhibited significantly higher scores on DASH questionnaire than those with three or fewer years of experience. This suggests that a longer duration of e-sports engagement may increase the likelihood of experiencing hand function problems and upper extremity injuries. Moreover, the study also found a significant difference in dominant hand strength between individuals with longer versus shorter e-sports experience. However, no significant differences were observed in non-dominant hand strength, hand function, or pain levels between the two groups.

The world of e-sports has seen exponential growth in recent years, with professional players competing at the highest levels and capturing the attention of millions of fans worldwide (24). However, behind the thrilling matches and electrifying moments lies a physical challenge that many e-sports athletes face musculoskeletal pain (25). Engaging in long hours of practice and intense gameplay sessions can take a toll on the body, resulting in various musculoskeletal issues. The repetitive movements and prolonged periods of static positioning can lead to discomfort and pain in different areas of the body, particularly the neck, shoulders, wrists, and hands. Recognizing the prevalence of musculoskeletal pain in e-sports players, it is crucial to address these issues proactively (10). The survey study conducted by Lindberg et al. (13), on 188 athletes examined the effect of e-sports experience on musculoskeletal health in e-sports players. Its objective was to assess the relationship between e-sport experience and musculoskeletal pain. The findings revealed no statistically significant association between sports experience duration and pain ($p>0.05$). However, it was observed that athletes with pain reported significantly lower e-sports training hours during the e-sport experience period (mean difference -5.6 hours/week; 95% CI -10.6 to -0.7, $p=0.035$). No statistically significant relationship was found between e-sport experience and musculoskeletal pain ($p>0.05$). However, it was observed that athletes with pain reported significantly lower e-sports training hours during the e-sport experience period (mean difference -5.6 hours/week; 95% CI -10.6 to -0.7, $p=0.035$). In the referenced study conducted by Fathuldeen et al. (14), which utilized self-reported pain locations and a questionnaire to assess the prevalence of musculoskeletal injuries in e-sports players, the most frequently reported pain regions were the lower back (63.8%), neck (50%), hand/wrist (44.8%), shoulder (35.3%), and upper back (27.6%). Additionally, the study examined the duration of participating in competitive video games among the respondents, revealing that 15.5% had been involved for 1-5 years, 17.2% for 6-10 years, and a majority of 67.2% for more than 10 years. In this research, participants with an e-sports experience duration of ≤ 3 years had an average VAS value of 2.75 ± 0.71, while those with ≥ 4 years of experience had a higher average VAS value of 3.50 ± 1.00. However, this difference was not statistically significant ($t=-1.831$, $p=0.084$, Table 2). Furthermore, there was a positive, moderate, and statistically significant relationship between e-sports experience in years and VAS ($r=0.591$, $p=0.006$, Table 3). Additionally, a positive, weak, and statistically significant relationship was found between daily e-sports time (hours) and VAS ($r=0.472$, $p=0.035$, Table 3). Considering the specific findings of the second study, which identified hand/wrist pain as a prevalent issue in e-sports players, and the established relationships in this research, it becomes evident that prolonged gaming can lead to increased discomfort and potential functionality issues in the hand and wrist. In a other study conducted by Di Francisco et al. (17), an electronic survey about the health habits and lifestyles of e-Sport athletes revealed that players practiced between 3 to 10 hours per day. The most frequently reported complaints were eye fatigue (56%), neck and back pain (42%), and hand and wrist

pain (36% and 32%, respectively). Interestingly, 40% of the participants did not engage in any form of physical exercise. The current study indicated a positive, moderate, and statistically significant correlation between the duration of e-Sport experience and VAS scores (r=0.591, p=0.006, Table 3). Additionally, there was no statistically significant difference in VAS scores when comparing participants with ≤3 years and those with ≥4 years of e-sports experience (t=-1.831, p=0.084, Table 2). These results highlight the influence of experience as a crucial factor in the health and pain status of e-sports athletes. This study contributes valuable insights in this regard, its under-scores the significance of experience in the field of e-sports connection between extended e-sports engagement and the escalation in self-reported pain levels.

Esport require rapid speed and reaction time, fine motor hand–eye coordination and demand high amounts of executive function and simultaneous actions. Therefore, hand function including manual dexterity and hand coordination skills enable e-sports athletes to execute complex and precise movements with speed and accuracy significantly impacting their overall performance and game outcomes (23). Tarannum et al. (27), explored the disparities in hand dexterity and skill between college students who actively engaged in mobile gaming and those who did not. The researchers utilized the Jebsen Taylor Hand Function Test to assess hand dexterity. The results revealed that gamers exhibited higher levels of right-hand dexterity, with an average value of 37.803 seconds (±3.4313), and left-hand dexterity, with an average value of 50.02 seconds (±4.101). In contrast, this study findings showed that non-gamers displayed right hand dexterity with an average value of 38.15 seconds (±4.3043), and left-hand dexterity with an average value of 50.921 seconds (±6.1409). The observed differences in hand coordination between the groups were statistically significant (p=0.001) for both right and left-hand dexterity. Furthermore, the statistical analysis confirmed that there were no significant differences in hand function including coordination between groups according to the experience for both dominant and non-dominant measurements (p=0.252, Table 2). Enhancing hand coordination and manual dexterity consider a crucial factor in optimizing e-sports performance. Additionally, the correlations between e-sports experience and daily e-sports time with the Purdue Pegboard Test measurements were non-significant (p>0.05, Table 3).

Upper extremity injuries in the esports players most likely result from chronic microtraumas rather than acute processes. Thus, the general health, upper extremity function and performance of the players are affected due to upper extremity disabilities as well as training effectiveness may be affected (28). Andersen et al. (29), examined the effects of different strength training frequencies and durations on neck and shoulder pain, as well as DASH scores, in office workers. The study included a total of 447 participants who were randomly allocated to one of four groups: 1WS: 1 hours training once a week; 3WS: 20 min training three times a week; 9WS: 7 min training nine times a week of supervised high-intensity strength training and a reference group without training. The results of the study revealed significant reductions in DASH scores among participants in the 1WS and 3WS groups compared to the reference group. Specifically, the 1WS group experienced an average decrease of 4 in DASH scores (p<0.05), while the 3WS group had a greater reduction with an average decrease of 7 (p<0.05). These findings suggest that engaging in specific strength training programs for one hour per week or three times a week for 20 minutes each can lead to significant improvements in functional disability, as measured by DASH scores. In line with these findings, this study focusing on e-sports athletes revealed a positive, albeit weak, but statistically significant correlation between the duration of e-sports experience in years and DASH scores (r=0.443; p=0.049, Table 3). This means that in e-sports experience increases, DASH scores may also increase, indicating a higher level of disability in the hands.

Additionally, a noteworthy observation from the study was the significant difference in DASH scores concerning e-sports experience duration. Participants with ≥4 years of e-sports experience had significantly higher DASH scores than those with ≤3 years, suggesting more hand problems (t=-2.203, p=0.041, Table 2). This finding establishes an association between extended e-sports participation and increased hand issues. These trends suggest that both prolonged experience in e-sports and extended daily engagement might potentially exacerbate hand problems, with the function parameter being negatively affected.

The strength parameter holds significant importance for e-sports and e-sports athletes. E-sports is a competitive activity that requires high-performance abilities, making power a critical factor in enabling players to excel during gameplay with long hours. Additionally, e-sports athletes engage in intense movements requiring prolonged concentration, highlighting the significance of power as an indicator of fatigue resistance (30). In study conducted by Fifolato et al. (31), which aimed to investigate the association between hand muscle strength, fatigue resistance, work ability, and hand dysfunction, several measurement methods were utilized. The results revealed moderate correlations between muscle strength (abduction: r = 0.49, adduction: r = 0.40, internal rotation: r = 0.44) and hand grip strength (r = 0.68) with Functional Impairment Test Hand and Neck/Shoulder/Arm (FIT-HANSA), indicating a positive association between power and fatigue resistance. Furthermore, hand grip strength showed a moderate correlation (r = -0.52) with hand dysfunction, highlighting its impact on functional abilities. In this study, there was a significant impact of power on hand function ($p < 0.01$, r = 0.72, Table 3), suggesting that enhanced strength levels were related to better hand function performance. When the relationship between e-sports experience and dynamometer measurements for the dominant hand was examined that statistically significant differences were found between both groups (t=- 2.101, p=0.049, Table 3). These differences demonstrate higher measurements for participants with ≥4 years of e-sports experience compared to those with ≤3 years of experience. Interestingly, the correlations between the duration of e-sports experience (in years) and daily e-sports duration (in hours) with dynamometer measurements were generally weak and non-significant ($r<0.35$ and $p>0.05$, Table 2). This result suggests that the duration of e-sports experience may impact dominant hand strength more than non-dominant hand strength, possibly due to the greater usage and control often exercised by the dominant hand in e-sports activities.

The current study provides valuable insights into the relationship between e-sports experience and hand function, disability, strength, coordination, manual dexterity and pain in male e-sports players. The fast-paced nature of e-sports competitions often means players must perform rapid and repetitive actions, such as clicking buttons or moving the mouse with precision. These repetitive movements can lead to overuse injuries and strain on the muscles and tendons involved, resulting in pain and reduced performance. Moreover, the competitive nature of e-sports can drive players to push their limits and ignore warning signs from their bodies. Players may disregard discomfort or pain in order to meet training demands or compete in important tournaments, further exacerbating the risk of musculoskeletal injuries. Understanding the health parameters (function, disability, pain, strength, coordination) of body regions for potential musculoskeletal injuries and seeking timely medical attention can prevent minor discomfort from escalating into chronic conditions that may affect both performance and long-term well-being (12, 32,33).

To the best of our knowledge, there is no study in the literature showing that investigates the association between e-sports experience and hand function, disability, strength, hands' skills (coordination & manual dexterity) and pain in esports players. Additionally, this study is also the first study to examine hand function, disability, strength, hands' skills (coordination

&manual dexterity) and pain with comparing experience duration among esports athletes. However, the few limitations should be acknowledged when interpreting the findings. Although the sample size obtained because of power analysis has been reached, only 20 participants limit the generalizability of the results and makes it difficult to draw definitive conclusions. A larger ample size in future studies would increase statistical power and better represent the e-sports population. Additionally, future research should aim to include a more diverse sample of e-sports players to provide a more representative picture of the population. Lastly, future studies should focus on exploring a wider range of variables, including reaction time, visual acuity, and mental health measures, which could lead to a more comprehensive understanding of the factors influencing e-sports performance and player well-being. In summary, while the study contributes valuable information to the understanding of the e-sports population, future research could build on this study findings by addressing these limitations and exploring a wider range of variables.

CONCLUSION

This study contributes valuable insights into the relationship between e- sports experience, hand function, and perceived pain among e-sports players. By understanding these outcomes, strategies can be developed to promote the well-being of e- sports players, optimize their performance, and ensure the sustained growth and success of the e-sports industry. Furthermore, the study shed light on the role of experience in e-sports. On the other hand, health parameters (function, disability, pain, strength, coordination) are a real concern for e-sports players due to the physical demands and prolonged hours of gameplay. By prioritizing proper ergonomics, self-care, and seeking professional guidance when needed, players can mitigate the risk of musculoskeletal injuries, promote longevity in their careers, and ensure a sustainable and healthy future in the dynamic world of e-sports.

Declarations

Conflict of Interest: The authors whose names are listed have no any conflicts of interest, containing financial or personal relationships with other people or organisations that could inappropriately affect (bias) their work.

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The Impact Of The Düzce Earthquake On Emergency Department Patient Load And Process Management

Düzce Depreminin Acil Servis Hasta Yükü Ve Süreç Yönetimi Üzerindeki Etkisi

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Abstract

Objective: Emergency health services are important in increasing the chance of survival of the sick and injured and preventing deaths during earthquakes and natural disasters.Within the scope of this research, we aimed to analyze the emergency service admissions during the Düzce Gölyaka earthquake disaster in November 2022 and improve our efficiency in the emergency service and trauma room.

Method: A total of 31 patients applied to Sakarya Training and Research Hospital following the 5.9 magnitude earthquake that occurred in the Gölyaka district of Düzce have been enrolled in this retrospective analysis. The trauma mechanism the patients were exposed to following the earthquake, the duration of admission to the hospital, the pathology detected, the treatment applied, the consultations requested, and the hospitalization or discharge status were recorded andanalyzed.

Results: Within the scope of the study, 31 patients affected by the earthquake were evaluated. The ages of the patients ranged from 12 to 75, with a mean age of 37 years. The gender distribution of the patients was as follows: 12 (38.7%) female and 19 (61.3%) male. The distribution of demographic and clinical findings according to the time of admission to the hospital is elaborated in Table 1. When the table is examined,it was determined that there was a statistical difference between the two groups regarding hospitalization, discharge, surgical procedure, and soft tissue trauma within 0 – 1 hour and 1 – 6 hours of admission ($p<0.05$).

Conclusion: In the face of this extremely diverse and severe patient profile, the presence of well-trained and experienced personnel in disaster medicine in emergency services and the presence of pre-preparedness can reduce mortality and morbidity in future disasters. The main purpose of emergency aid is to save many human lives in a short time and to meet basic urgent needs.

Keywords: Earthquake, Emergency Service, Trauma Room, Triage, Disaster Management.

Özet

Amaç: Acil sağlık hizmetleri, deprem ve doğal afetlerde hasta ve yaralıların yaşama şanslarının artırılması, ölümlerin önlenmesi açısından önemlidir. Bu araştırma kapsamında Kasım 2022'de Düzce Gölyaka deprem felaketi sırasında acil servis başvurularını analiz ederek acil servis ve travma odasında süreçlerimizi verimlilik açısından iyileştirmeyi amaçladık.

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Yöntem: Düzce'nin Gölyaka ilçesinde meydana gelen 5.9 büyüklüğündeki depremin ardından Sakarya Eğitim ve Araştırma Hastanesi'ne başvuran toplam 31 hasta retrospektif olarak yapılan bu analize dahil edildi. Hastaların deprem sonrası maruz kaldıkları travma mekanizması, hastaneye yatış süreleri, saptanan patoloji, uygulanan tedavi, istenen konsültasyonlar, hastanede yatış veya taburcu olma durumları kayıt altına alınarak analiz edildi.

Bulgular: Çalışma kapsamında depremden etkilenen 31 hasta değerlendirildi. Hastaların yaşları 12 ile 75 arasında değişmekte olup, ortalama yaş 37'dir. Hastaların cinsiyet dağılımı 12 (%38.7) kadın, 19 (%61.3) erkek olarak bulundu. Başvuru süresine göre gruplandırılan hastalarda iki grup arasında hastaneye yatış, taburculuk, cerrahi girişim ve yumuşak doku travması0 – 1 saat ve 1 – 6 saat başvuru süreleri arasındaistatistiksel anlamlı farklılık saptanmıştır ($p<0.05$).

Sonuç: Deprem sırasında birbirinden farklı ve ağır hasta profili karşısında, acil servislerde afet hekimliği konusunda iyi eğitimli ve deneyimli personelin bulunması ve önceden hazırlıklı olunması, gelecekteki afetlerde mortalite ve morbiditeyi azaltabilir. Acil yardımın temel amacı kısa sürede çok sayıda insanın hayatını kurtarmak ve temel acil ihtiyaçları karşılamaktır.

Anahtar Kelimeler: Deprem, Acil Servis, Travma Odası, Triyaj, Afet Yönetimi.

INTRODUCTION

Although earthquakes can occur in any place and time, the places where they are seen intensely constitute three main belts. These are Pacific Seismic Belt, Alpine-Himalayan Seismic Belt, and Atlantic Seismic Belt (1). Turkey is located on the Alpine-Himalayan Earthquake Belt, which is one of the most active of these. Since we are located on this belt and in the region where the tectonic plates intersect, it can be said, based on the information of the past years our country is a major zonefor earthquakes on average every five years, causing extensive loss of life and property (2).

Considering that medical emergencies, violent events, and disasters frequently occur today, Emergency health services are important in increasing the chance of survival of the sick and injured and preventing deaths (3). Regardless of their social and economic status, people need emergency health care in the best possible way when they encounter emergencies. The way to provide instant health service to everyone in need is to establish a central organization. Providing the service from a single source will achieve minimum cost and maximum gain (4). Thanks to this organization, in the event of a disaster, it will be more possible to ensure the safety of the victims' lives and then meet their basic needs such as food and shelter. One of the main objectives is that the interventions to be made are programmed, sustainable, and practices that strengthen the society's resources (5).

It should be remembered that all health institutions will be overloaded in the first hour or minutes because of the patients who reach the emergency services. However, patients requiring major or intensive care will come from the rear as the debris is removed or from other nearby villages. For this reason, it is necessary to direct the patients to the emergency room quickly (6). According to the triage rules, the slightly injured are immediately sent to the outpatient clinics. No time is wasted for patients whose condition is very bad and who have no chance of survival. Because the aim is to help more injured people with limited means, the senior doctor in charge of triage can decide this by looking at the patient's face. The patients do not request blood tests, and X-rays are not taken unless necessary. For example, if a fracture is not very complicated, it is just splinted and sent home, anddefinitive treatment is performed the next day (7).

One of the groups that should be given the most importance in disaster situations is the media, and the other is the relatives of the patients. Both groups are right in their expectations. Media members must inform the public by passing the most accurate news to their center as soon as

possible. But this requirement should allow doctors to work properly (8). For this reason, a center with a very good communication network should be established in the hospital. The hospital's social worker constantly conveys fresh and accurate news to these people. A constant flow of information should be ensured by establishing a center within the hospital for the accompanying persons. In other words, people who are not sick should be prevented from entering the patient care area (8 – 10).

Within the scope of this research, we aimed to analyze the emergency service admissions during the Düzce Gölyaka earthquake disaster in November 2022 and improve our processes in terms of efficiency in emergency service and trauma room. We believe the outcomes of this study will provide a road map for emergency service management measures following natural disasters.

METHOD

A total of 31 patients applied to Sakarya Training and Research Hospital following the 5.9 magnitude earthquake that occurred in the Gölyaka district of Düzce have been enrolled in this retrospective analysis.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 216243-29, andinformed consent has been obtained from all participants.

The trauma mechanism the patients were exposed to following the earthquake, the duration of admission to the hospital, the pathology detected, the treatment applied, the consultations requested, and the hospitalization or discharge status were recorded andanalyzed.Emergency service application hours (0 – 1. hour and 1 – 6. hours) were also examined in line with the records.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data was given as descriptive values. "Independent Sample T-Test" was used to compare groups, and "Fisher's Exact Test or Chi-Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Within the scope of the study, 31 patients affected by the earthquake were evaluated. The ages of the patients ranged from 12 to 75, with a mean age of 37years. The gender distribution of the patients was as follows: 12 (38.7%) female and 19 (61.3%) male.

The distribution of demographic and clinical findings according to the time of admission to the hospital is elaborated in Table 1. When the table is examined,it was determined that there was a statistical difference between the two groups regarding hospitalization, discharge, surgical procedure, and soft tissue trauma within 0 – 1 hour and 1 –6 hours of admission ($p<0.05$).

Table 1. Distribution of Demographic and Clinical Findings by Patients' Application Times

	Total (N=31)	Application Time (0 – 1 hour) (n=14)	Application Time(1 – 6 hours) (n=17)	p-value
	n (%) or Median±SD	n (%) or Median±SD	n (%) or Median±SD	
Age *(years)*	37±19	36±23	38±16	0.842
Gender				0.496
Female	12 (38.7)	4 (28.6)	8 (47.1)	
Male	19 (61.3)	10 (71.4)	9 (52.9)	
Reason for application				
Fall	22 (71)	9 (64.3)	13 (76.5)	0.693
High jump	6 (19.4)	3 (21.4)	3 (17.6)	1.000
Hitting object	2 (6.5)	1 (7.1)	1 (5.9)	1.000
Extremity injury	22 (71)	11 (78.6)	11 (64.7)	0.456
Thoracic trauma	2 (6.5)	0 (0)	2 (11.8)	0.488
Head trauma	4 (12.9)	3 (21.4)	1 (5.9)	0.304
Orthopedic emergencies	19 (61.3)	11 (78.6)	8 (47.1)	0.155
Upper Extremity **Fracture**	6 (19.4)	4 (28.6)	2 (11.8)	0.370
Lower Extremity **Fracture**	8 (25.8)	3 (21.4)	5 (29.4)	0.698
Shoulder dislocation	2 (6.5)	2 (14.3)	0 (0)	0.196
Calcaneus Fracture	3 (9.7)	2 (14.3)	1 (5.9)	0.576
Vertebral Fracture	1 (3.2)	1 (7.1)	0 (0)	0.452
Intracranial Hemorrhage	2 (6.5)	2 (14.3)	0 (0)	0.196
Linear Fracture	1 (3.2)	1 (7.1)	0 (0)	0.452
Cot Fracture	1 (3.2)	0 (0)	1 (5.9)	1.000
Consultation unit				
Neurosurgeon **Consultation**	2 (6.5)	2 (14.3)	0 (0)	0.196
Orthopedics Consultation	14 (45.2)	9 (64.3)	5 (29.4)	0.114
Surgeon General Consultation	3 (9.7)	3 (21.4)	0 (0)	0.081
Eye Consultation	1 (3.2)	1 (7.1)	0 (0)	0.452
Admission	6 (19.4)	**6 (42.9)**	**0 (0)**	**0.004**
Discharge	25 (80.6)	**8 (57.1)**	**17 (100)**	**0.004**
Intensive care	2 (6.5)	2 (14.3)	0 (0)	0.196
Surgical	5 (16.1)	**5 (35.7)**	**0 (0)**	**0.012**
Plaster Splint	14 (45.2)	7 (50)	7 (41.2)	0.898
Incision Suture	6 (19.4)	5 (35.7)	1 (5.9)	0.067
Soft tissue trauma	13 (41.9)	**2 (14.3)**	**11 (64.7)**	**0.014**

DISCUSSION

Earthquakes differ from other natural disasters in that they are sudden-onset and destructive. Due to its complex geological structure and geodynamic location, Turkey is one of the regions where earthquakes are most common worldwide, containing many active fault lines.Earthquakes have injured and killed millions of people (11). Adequate and well-timed management by rescuers and health professionals can contribute to reduced disability and death. In earthquakes, the services provided by health professionals are often delayed due to the destruction of roads, damage to hospitals, and inadequate equipment (12).

After the earthquake, there was an increasing number of applications to the emergency health services from the first hours, both due to being under the s with the effect of the devastation and injuries that may occur when people move away from their environment in case of panic caused by a natural disaster (13). It was concluded that crush and sprain injuries, such as soft tissue trauma, are common in injuries caused by earthquakes, and the need for surgical procedures and hospitalization rates in earthquake victims who applied to the hospital within the first hour after the event was significantly higher than those admitted after the first hour. It was concluded that it would be appropriate to plan the emergency service in this direction, considering that there will be more patient admissions, especially in the first hours after the earthquake, and these cases may be complicated cases requiring hospitalization or surgery (14).

In the management of post-earthquake emergency health services, Turkey's Disaster Response Plan at the national level and the National Level Health Service Group Plan; at the local level, Provincial Disaster Response Plans, Local Level Health Service Group Plans, and Hospital Disaster and Emergency Plans have been preparedto clarify the implementation. The main solution partner of the Health Service Group is the Ministry of Health. On the other hand, its responsibility is to coordinate to meet the needs of first response, public health and medical care at the scene in disasters and emergencies and to ensure that environmental health services return to normal as quickly as possible without interruption (15).

The Van Earthquake that took place in 2011 can be considered an example of post-earthquake emergency health services in our country. With the occurrence of the earthquake, SAKOM convened urgently and continued its work on a 24-hour basis. 112 Emergency Medical teams and UMKE personnel in the city center and its districts arrived at the scene in the first 20 minutes. A total of 2.905 health personnel participated, and 24% of them started to work at the scene within the first 24 hours. Again in the first 24 hours, 113 ambulances were on duty. It corresponds to approximately 75% of the ambulances in total. Within the scope of health services,six field hospitals were established in addition to the four hospitals that were not damaged, six field hospitals. UMKE and ambulance teams were present at all the wrecks that were rescued. UMKE teams personally participated in 252 live rescue efforts in both earthquakes and played a major role in transferring 1403 to other provinces by land ambulances and 271 patients by air ambulances (16).

The Hospital Disaster Plan (HAP) was published and put into effect on 20.03.2015 in order to improve the hospital capacity in emergencies and disasters, increase sustainability, increase the service, prevent the panic environment, to make the intervention fast and effective; in short, to ensure that the hospitals are prepared for disasters and emergencies (HAP, 2015). Medical assistance in disasters in Turkey is provided by 112 ambulance teams, UMKE, and other institutions and NGOs participating in the scene. Studies in Turkey started with the Hospital Disaster Plans issued in 2015. Once the disaster occurs, the HAP protocol is applied (17).

A hospital disaster command center should be established once the news is received. Emergency services and all hospital unitsshould be activated according to the plan. Security teams keep the vehicle and human traffic in the hospital under control. Special departments established for the media and patient relatives should initiate a suitable communication network. Continuous coordination is ensured with the city disaster command center, and a person is assigned for this task. One of the most important rules of success in patient care is serious triage practices. Hospitals should have written disaster plans,which should be read and learned very well by those with a duty (in case of a disaster, there is no time to read them, even these books cannot be found to be read). These plans should be tested at least twice yearly (10, 18).

After those hectic moments of the disaster are over, the hospital and especially the emergency service should be restored quickly. Because daily life will be restored, patients will continue to come, or a new disaster may occur at any moment. After that, the hospital's top management should meet with the relevant people to review the failing points and correct the observed deficiencies quickly, without a new disaster (19, 20).

CONCLUSION

In the face of this extremely diverse and severe patient profile, the presence of well-trained and experienced personnel in disaster medicine in emergency services and the presence of pre-preparedness can reduce mortality and morbidity in future disasters.Emergency aid, identifying those affected by the disaster, debris removal, injured rescue, medical first aid and treatment, evacuation, meeting basic vital needs such as shelter, nutrition, protection, heating, communication, psychological support, providing security to prevent chaos and disorder, administrative and activities for the provision of technical support services should be professionally organized. The main purpose of emergency aid is to save many human lives in a short time and to meet basic urgent needs.

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Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution.As this was a retrospective research, no informed consent has been obtained from participants.

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Evaluating the Frequency of Academic Procrastination and Associated Factors in the Academic Population

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Abstract

Background: There are few people who do not delay in their daily lives. Procrastination behavior is a very common problem we face in also academic life.
Aim: In this study we aimed to elucidate the frequency of academic procrastination and associated factors in the academic population.
Method: This study includes 306 volunteer participants who work as professors, associate professors, doctors, lecturers, research assistants and lecturers at Balıkesir University. Aitken Academic Procrastination Scale, Spielberg State-Trait Anxiety Scale, Brief Symptom Inventory, Rosenberg Self-Esteem ScaleandHewitt Multidimensional Perfectionism Scalewere applied to all participants. The sociodemographic data form and all the other scales were filled in by the participant himself.
Results: According to the findings of the study, the frequency of academic procrastination in the academic population is %48. Among the socio-demographic variables; age and academic duration were found to be associated with academic delay. The groups with high academic procrastination were found to have higher levels of state-trait anxiety; mental symptoms such as depression and somatization were found more common. A negative relationship was determined between self-focused perfectionism and academic procrastination in the academic population.
Conclusion: This research was a pioneer study conducted in the academic population compared to previous literature. Regarding the outcomes one can conclude that seniority in academic profession and age has positively affected the endurance of the individual while tendency to anxiety and self-focused perfectionism increased procrastination behavior.

Keywords: Academic Procrastination, Depression, Anxiety, Perfectionism.

INTRODUCTION

Procrastinationis a consequence of choices. This decision often persists despite numerous opportunities to modify the existing model (1). The behavior of procrastination, which is initially pleasant for the person; becomes a habit accompanied by emotional anxiety, worry, feelings of inadequacy and unhappinessover time (2).

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Postponement is handled in two parts; the first is "procrastination as a personality trait" or "chronic procrastination" and the second is "situational procrastination" (3). Procrastination as a personality trait can be shown in many areas, which can cause feelings of inadequacy and helplessness in the process of coping with his environment, compulsive procrastination, procrastination, and neurotic procrastination. Situational procrastinationoccurs in certain periods of life, is not typical, is less common than procrastination, which is seen as a personality trait, and has two sub-dimensions: general procrastination and academic procrastination (4,5). Psychiatric problems may stand out as both the cause and the result of the procrastination process (6). Anxiety is one of these problems among the main reasons for academic procrastination (7).

As the procrastination behavior increases, the anxiety of the individual increases (8). In studies conducted with adults, significant positive relationships were observed between academic procrastination and anxiety (9,10). Researchers questioning the reasons for procrastination have examined the relationship between procrastination and self-esteem. Individuals with a high procrastination behavior in delaying starting or completing a task fear failure and evaluation for their own performance and abilities (6).

In many academic procrastination studies, significant negative relationships were found between self-esteem and academic procrastination (11,12). Individuals who procrastinate can spend less effort on their duties and leave their jobs more quickly so that their self-esteem is not further negatively affected (13).

Another important predictor of academic procrastination has been evaluated as a perfectionist personality trait. Studies in this direction have mostly been carried out according to the perfectionism dimensioned by Hewitt and Flett (14). This dimensioning includes self-focused perfectionism, others-oriented perfectionism, and socially orientedperfectionism. Self-focused perfectionisminvolves the individual setting high standards for himself, evaluating his own behavior strictly, and disapproving of his behavior.Othersoriented perfectionism includes expectations and beliefs about the capabilities of others. Socially oriented perfectionism includes the belief and perception that others have high standards for themselves and are pressured by others to be perfect (14). Self-focused perfectionists have a tendency to approach situations that require success. They are meticulous in their work and motivate themselves to achieve perfection. They try to perfect their action to avoid failure (14).

There is a negative relationship between procrastination and socially oriented perfectionism. Since the standards imposed by others are considered more than normal and uncontrollable, reactions such as tension, anxiety, depression, and failure may occur in the person. This situation may present itself with a positive relationship with procrastination behavior (15).

The number of people who do not procrastinate in daily life is almost negligible. Procrastination is a very common problem in academic life. When the literature was examined, it was seen that studies on academic procrastination were conducted in high school and university students (16-18) rather than academicians.

Study Hypothesis

Thenumber of peoplewho do not procrastinate in daily life is almostnon-existent. Procrastination is a verycommon problem in academic life. Inacademics, thestudy of academicprocrastinationdid not standout in theliterature.

Therefore, in this study, we tried to elucidate the frequency of academic procrastination and the factors that may be associated with academicians who work as professors, associate professors, doctoral faculty members, lecturers, research assistants, lecturers in the academic units of Balıkesir University.

METHOD

A total of 306 academicians have been enrolled in this study. The study group consisted of academic staff of both genders working as professors, associate professors, doctoral lecturers, lecturers, research assistants and lecturers in different education units at Balıkesir University. The ethics committee approval has been granted at 09.10.2019, protocol number 2019 – 140.

In the first stage, male and female participants were divided into 2 groups and compared with respect to clinical variables. According to the Aitken academic procrastination scale, the participants were divided into two groups as low academic procrastination (Group-1) (52% and n=159) and high academic procrastination (Group-2) (48% and n=147).

Sociodemographic data form, Aitken Academic Procrastination Scale (AAPS), Spielberg State-Trait Anxiety Inventory (STAI-1, STAI-2), Brief Symptom Inventory (BSI), Rosenberg Ego Respect Scale (RERS) and Hewitt Multidimensional Perfectionism Scale (HMDPS) were applied. The sociodemographic data form and all other scales were filled in by the participant himself.

Statistical Analysis

Statistical analyzes were performed using the SPSS Statistics 20.0 package program. In our study, Skewness and Kurtosis values were examined to determine whether the groups showed a normal distribution. Skewness value is between 0.439-0.139; Kurtosis value, on the other hand, was observed to vary between -0.307-0.278 and was considered to have a normal distribution. Pearson Correlation analysis was applied to reveal the relationship between the groups. T test was used for difference analysis, and those with a p value less than 0.05 were considered significant.

RESULTS

A total of 306 volunteers, 155 women (50.7%) and 151 men (49.3%) from the academic staff of Balıkesir University had participated in this study. The academical titles of the individuals were as follows: 14.1% of them (n=43) were professors, 16.7% (n=51)of them were associate professors,27.1% (n=83)of them were physicians, and5.9% of them were (n=18) lecturers. The mean range was 23-67 years (ranging between 37.79±8.914 years) and the mean academic profession time was 1-44 years (ranging between 10±9.086 years).

According to the age variable, the difference between men and women was not significant. The mean score of academic procrastination tendency scale and STAI-1 was not significant between the groups.On the contrary, the mean score of STAI-2 was statistically significant between female (40.09±9.873) and male (37.52±9.073) individuals (t=2.367 and p=0.019) (Table1).

The participants were divided into two groups as low academic procrastination (Group-1: 52% and n=159) and high academic procrastination (Group-2: 48% and n=147). According to the Aitken Academic Procrastination scale the difference between the groups was statistically significant (t=2.988 and p=0.003) in terms of age (Group 1: 39.23 years versus Group 2: 36.22 years) (Table2).

Table 1. Comparison of Variables by Gender

	Groups	N	Mean	SD	P	T
Gender	Female	155	33.53	11.09	-0.678	0.498
	Male	151	34.4	11.453	-0.677	0.498
Age	Female	155	37.56	8.819	0.654	-0.449
	Male	151	38.02	9.033	0.654	-0.449
Academic Profession Duration	Female	155	11.61	9.072	0.218	1.234
	Male	151	10.33	9.085	0.218	1.233
AAPS	Female	155	33.53	11.09	0.498	-0.678
	Male	151	34.4	11.493	0.499	-0.677
STAI – 1	Female	155	36.32	10.852	0.275	1.093
	Male	151	35.02	9.962	0.275	1.094
STAI – 2	Female	155	40.09	9.873	0.019	2.367
	Male	151	37.52	9.073	0.018	2.369
BSI – A	Female	155	5.78	7.198	0.798	0.256
	Male	151	5.57	7.216	0.798	0.256
BSI – D	Female	155	8.1	8.163	0.369	0.9
	Male	151	7.27	7.877	0.369	0.9
BSI – S	Female	155	3.83	4.524	0.075	1.787
	Male	151	2.93	4.263	0.075	1.789
BSI – H	Female	155	4.41	4.718	0.792	-0.264
	Male	151	4.55	4.79	0.792	-0.263
BSI – O	Female	155	6.29	7.578	0.95	-0.062
	Male	151	6.34	7.609	0.95	-0.062
RERS	Female	155	0.8511	0.68019	0.237	1.185
	Male	151	0.76	0.66536	0.237	1.185
EXCELLENCE – SF	Female	155	87.7	17.849	0.936	0.08
	Male	151	87.52	19.855	0.936	0.08
EXCELLENCE – S	Female	155	53.94	13.025	0.61	-0.511
	Male	151	54.63	10.314	0.609	-0.512
EXCELLENCE – B	Female	155	43.77	10.555	0.611	-0.509
	Male	151	44.38	10.399	0.611	-0.509

AAPS: Aitken Academic Procrastination Scale, STAI-1: Spielberg State-Trait Anxiety Inventory – I, STAI-2: Spielberg State-Trait Anxiety Inventory – II, BSI: Brief Symptom Inventory, BSI-A: Anxiety, BSI-D: Depression, BSI-S: Somatization, BSI-H: Hostility, BSI-O: Negative Self, RERS: Rosenberg Ego Respect Scale, EXCELLENCE-SF: Self-Focused Perfectionism, EXCELLENCE-S: Socially Oriented Perfectionism, EXCELLENCE-B: Others-Focused Perfectionism.

The duration of academic profession average was significant, 12.72 years in Group-1 and 9.1 years in Group-2. The difference between the groups according to the STAI-1 variable was significant,33.93 in Group-1 and 37.57 in Group-2 (t=-3.095 and p=0.002). The STAI-2 score average was 36.44 in Group-1 and 41.40 in Group-2 (t=-4.69 and p=0.000) (Table2).

Table 2. Comparison of the Groups with Low (1) and High (2) Academic Procrastination Tendency

	Groups	N	Min	Max	Mean	SD	T	P
Age	1	159	23	67	39.23	9.439	2.988	0
	2	147	23	56	36.22	8.052	3.006	0
Academic Profession Duration	1	159	1	44	12.72	9.904	3.554	0
	2	147	1	32	9.1	7.71	3.589	0
STAI – 1	1	159	18	69	33.93	9.841	-3.095	0.002
	2	147	20	71	37.57	10.739	-3.084	0.002
STAI – 2	1	159	21	79	36.44	8.99	-4.69	0
	2	147	22	63	41.4	9.513	-4.68	0
BSI – A	1	159	0	47	4.36	6.615	-3.372	0.001
	2	147	0	34	7.1	7.545	-3.355	0.001
BSI – D	1	159	0	48	6.61	7.948	-2.469	0.014
	2	147	0	34	8.86	7.962	-2.469	0.014
BSI – S	1	159	0	31	2.86	4.332	-2.159	0.032
	2	147	0	19	3.95	4.446	-2.157	0.032
BSI – H	1	159	0	27	4.01	4.838	-1.787	0.075
	2	147	0	19	4.98	4.609	-1.791	0.074
BSI – O	1	159	0	45	5.44	7.625	-2.116	0.035
	2	147	0	30	7.27	7.442	-2.118	0.035
RERS	1	159	0	4.67	0.7524	0.60132	-1.456	0.146
	2	147	0	4.5	0.8643	0.74117	-1.444	0.15
EXCELLENCE – K	1	159	37	126	91.69	18.758	4.039	0
	2	147	24	122	83.2	17.959	4.046	0
EXCELLENCE – S	1	159	21	94	54.01	12.413	-0.415	0.68
	2	147	18	83	54.57	11.025	-0.417	0.68
EXCELLENCE – B	1	159	14	63	45.17	10.586	1.923	0.055
	2	147	10	58	42.88	10.237	1.925	0.055

AAPS: Aitken Academic Procrastination Scale, STAI-1: Spielberg State-Trait Anxiety Inventory – I, STAI-2: Spielberg State-Trait Anxiety Inventory – II, BSI: Brief Symptom Inventory, BSI-A: Anxiety, BSI-D: Depression, BSI-S: Somatization, BSI-H: Hostility, BSI-O: Negative Self, RERS: Rosenberg Ego Respect Scale, EXCELLENCE-S: Self-Focused Perfectionism, EXCELLENCE-S: Socially Oriented Perfectionism, EXCELLENCE-B: Others-Focused Perfectionism.

BSI – Anxietyscore average was 4.36 in Group-1 and 7.1 in Group-2 (t=-3.372 and p=0.001). BSI – Depressionmean score was6.61 in Group-1 and 8.86 in Group-2, significant between the groups (t=-2.469 and p=0.014). BSI – Somatizationmean score was 2.86 in Group-1 and 3.95 in Group-2, significant (t=-2.159 and p=0.032).The mean BSI – NegativeSelf score was 5.44 in Group-1 and 7.27 in Group-2. The difference between the groups according to the BSI – Negativeself-variable was significant (t=-2.116 and p=0.035). Self-Focused Perfectionism mean score was statistically different between the groups, 91.69 in Group-1 and 83.2 in Group-2 (t=4,039 and p=0.00) (Table 2).

Table 3. Correlation Analysis of Group 1's Scores with the Academic Procrastination Tendency Scale and Related Factors

		AAPS	STAI1	STAI2	BSI-A	BSI-D	BSI-S	BSI-H	BSI-O	RERS	EXCELLENCE–K	EXCELLENCE–S	EXCELLENCE–B
RERS	R	1											
	P												
	N	159											
STAI – 1	R	,255**	1										
	P	,001											
	N	159	159										
STAI – 2	R	,240**	,673**	1									
	P	,002	,000										
	N	159	159	159									
BSI – A	R	,096	,645**	,699**	1								
	P	,231	,000	,000									
	N	159	159	159	159								
BSI – D	R	,157*	,645**	,731**	,856**	1							
	P	,048	,000	,000	,000								
	N	159	159	159	159	159							
BSI – S	R	,053	,542**	,623**	,758**	,708**	1						
	P	,505	,000	,000	,000	,000							
	N	159	159	159	159	159	159						
BSI – H	R	,119	,610**	,514**	,725**	,709**	,624**	1					
	P	,134	,000	,000	,000	,000	,000						
	N	159	159	159	159	159	159	159					
BSI – O	R	,187*	,598**	,678**	,838**	,869**	,650**	,766**	1				
	P	,018	,000	,000	,000	,000	,000	,000					
	N	159	159	159	159	159	159	159	159				
RERS	R	,063	,350**	,439**	,534**	,542**	,418**	,335**	,557**	1			
	P	,434	,000	,000	,000	,000	,000	,000	,000				
	N	159	159	159	159	159	159	159	159	159			
EXCELLENCE – K	R	-,064	,100	,053	,079	,052	,068	,173*	,170*	,152	1		
	P	,423	,212	,511	,323	,517	,395	,030	,032	,055			
	N	159	159	159	159	159	159	159	159	159	159		
EXCELLENCE – S	R	,126	,167*	,262**	,243**	,247**	,175*	,174*	,339**	,347**	,419**	1	
	P	,114	,035	,001	,002	,002	,027	,028	,000	,000	,000		
	N	159	159	159	159	159	159	159	159	159	159	159	
EXCELLENCE – B	R	,126	,167*	,262**	,243**	,247**	,175*	,174**,**	,339**,**	,347**	,419**	1,000**	1**
	P	,114	,035	,001	,002	,002	,027	,028	,000	,000	,000	0,000	,000
	N	159	159	159	159	159	159	159	159	159	159	159	159

The correlation was significant at the 0.01 level.

*** The correlation was significant at the 0.05 level.***

Table 4. Correlation Analysis of Group 2's Scores withthe Academic Procrastination TendencyScale and Related Factors

		AAPS	STAI1	STAI2	BSI-A	BSI-D	BSI-S	BSI-H	BSI-O	RERS	EXCELLENCE – K	EXCELLENCE – S	EXCELLENCE – B
RERS	R	1											
	P												
	N	147											
STAI – 1	R	,142	1										
	P	,087											
	N	147	147										
STAI – 2	R	,226**	,725**	1									
	P	,006	,000										
	N	147	147	147									
BSI – A	R	,217**	,572**	,609**	1								
	P	,008	,000	,000									
	N	147	147	147	147								
BSI – D	R	,252**	,595**	,690**	,840**	1							
	P	,002	,000	,000	,000								
	N	147	147	147	147	147							
BSI – S	R	,152	,466**	,499**	,760**	,698**	1						
	P	,066	,000	,000	,000	,000							
	N	147	147	147	147	147	147						
BSI – H	R	,107	,473**	,569**	,790**	,794**	,712**	1					
	P	,196	,000	,000	,000	,000	,000						
	N	147	147	147	147	147	147	147					
BSI – O	R	,219**	,544**	,607**	,867**	,850**	,723**	,787**	1				
	P	,008	,000	,000	,000	,000	,000	,000					
	N	147	147	147	147	147	147	147	147				
RERS	R	,280**	,273**	,467**	,535**	,446**	,370**	,388**	,528**	1			
	P	,001	,001	,000	,000	,000	,000	,000	,000				
	N	147	147	147	147	147	147	147	147	147			
EXCELLENCE – K	R	-,130	-,014	-,006	,042	,051	-,024	,080	,086	,014	1		
	P	,117	,866	,938	,612	,536	,772	,338	,300	,866			
	N	147	147	147	147	147	147	147	147	147	147		
EXCELLENCE – S	R	,152	,345**	,449**	,345**	,384**	,328**	,380**	,413**	,285**	,355**	1	
	P	,066	,000	,000	,000	,000	,000	,000	,000	,000	,000		
	N	147	147	147	147	147	147	147	147	147	147	147	
EXCELLENCE – B	R	,152	,345**	,449**	,345**	,384**	,328**	,380**	,413**	,285**	,355**	1,000**	1**
	P	,066	,000	,000	,000	,000	,000	,000	,000	,000	,000	0,000	,000
	N	147	147	147	147	147	147	147	147	147	147	147	147

***Thecorrelationwassignificant at the 0.01 level.*

** Thecorrelationwassignificant at the 0.05 level.*

In Group 1; a positive and significant relationship was found between the Aitken Academic Procrastination Scale, STAI-1 and STAI – 2scales. A positive and significant relationship was found between the Aitken Academic Procrastination Scale and the BSI sub – dimensionsof Depression and Negative Self score (Table 3).

In Group 2; a positive and significant relationship was found between the Aitken Academic Procrastination Scale and STAI – 2scales. A positive and significant relationship was found between the Aitken Academic Procrastination Scale and Depression, Anxiety and Negative Self sub-dimensions of the BSI scale. A positive and significant relationship was found between the Aitken Academic Procrastination Scale and the Rosenberg Self-Esteem Scale (Table 4).

DISCUSSION

Previously, studies that had been conducted with high school and university students have shown that the frequency of procrastination has reached up to 60% and above. The absence of studies in academic populationmakes it difficult to derive comparisons, thus making this study a pioneer in this era.

Ferrari and Beck reported that procrastinators felt more negative after making fraudulent excuses for work not completed on time (19). Tice and Baumeister stated that academic procrastinators reported lower stress and less illness at the beginning of the semester than non-procrastinators, but generally higher stress and more illness in the late period (20). The procrastination process can cause more stress to the person as the due date of the tasks that need to be done approached and required the completion of the task. The high levels of stress experienced due to this behavior might cause adverse immune changes that lead to an increased risk of disease (21,22).

According to the results of this study, the tendency to procrastinate was 48% in the academic population. Among the groups with high and low procrastination tendencies, the highest rate belongs to research assistants and doctoral faculty members.

According to Akdoğan and Deniz, academic procrastination average scores of university students differed significantly according to their depression, anxiety and stress levels. Due to the complaints of depression and anxiety, students' starting and maintaining their academic duties and responsibilities may be delayed or incomplete (23). It has been observed that studies on psychiatric symptoms such as somatization and hostility, in which sub-headings such as anxiety and depression were frequently examined, were insufficient in evaluating academic procrastination and related factors in the literature (24). In this study, it was observed that somatization affects academic procrastination, and this can be interpreted as depression or anxiety may cause somatic symptoms in individuals who procrastinate.

In the relationship between age and academic procrastination; It was concluded that academic procrastination tendency was negatively correlated with age. This result was in line with the studies in the literature (25-27). Similarly, a negative relationship has been found between academic profession time and procrastination. This might be an indication that individuals develop strategies to overcome or avoid procrastination over time (28).

In previous research, it was shown that there was no gender difference in academic procrastination (29) although some studies reported that male students had more academic procrastination tendency (30). In this study, no statistically significant difference was observed between gender and academic procrastination.

Academic procrastination behavior emphasized that anxiety was one of the leading reasons for procrastination (6,7). This situation has been elaborated in the literature examining the relationship between state and trait anxiety and academic procrastination (9,10,31,32). The relationship between academic procrastination and anxiety level is bidirectional, and anxiety has been defined as a condition that both causes procrastination and occurs after this behavior (6). According to the results of our study, it was found that statefulness and trait anxiety significantly predicted academic procrastination behavior.

Published research have shown that procrastination was linked to negative mental health conditions, including anxiety, depression and high stress perception (33). In this study, we have determined that while somatization, depression and anxiety affected academic procrastination behavior, hostility did not.

Researchers who investigated the causes of procrastination also tried to reveal the relationship between self-esteem and procrastination behavior. In many academic procrastination studies, significant negative relationships were found between procrastination tendency and self-esteem (34). In the literature, it was stated that the education factor was an effective variable on self-esteem and that self-esteem might increase with the increase in educational level (35). In this study, it was observed that self-esteem was not effective on academic procrastination behavior, and this difference showed that self-esteem was higher with the increased educational level.

In summary, we aimed to examine academic procrastination and related factors in the academic population. The frequency of academic procrastination was 48%. Age and academic duration from sociodemographic variables were found to be associated with academic procrastination. State and trait anxiety levels were higher in the group with procrastination tendency. Psychological symptoms such as depression and somatization were more common in the group with a high tendency to academic procrastination. It has been observed that self-esteem does not pose a risk for procrastination in academics. A negative correlation was found between self-focused perfectionism and academic procrastination in the academic population.

Limitations of the Study

The main limitation of the study could be attributed to the sample population obstacles. All academics working at Balıkesir University could not be included in the researh. In addition, the number of research assistant participants in the study group was higher compared to other studies.

Previously published studies on academic procrastination have been mostly conducted with high school and university students. The absence of data with the academic population makes this study a unique research. Detection of risk factors and accompanying psychiatric complaints related to procrastination in larger studies could contribute positively to the academic success of individuals.

CONCLUSION

This research was a pioneer study conducted in the academic population compared to previous literature. Regarding the outcomes one can conclude that seniority in academic profession and age has positively affected the endurance of the individual while tendency to anxiety and self-focused perfectionism increased procrastination behavior..

Informed consent: Informed consent has been obtained from all the patients before the initiation of the study.

Institutional Review Board Approval: The ethics committee approval has been granted at 09.10.2019, protocol number 2019 –140.

Abbreviations

AAPS	: Aitken Academic Procrastination Scale
BSI	: Brief Symptom Inventory
CI	: confidence interval
EXCELLENCE-B	: Others-Focused Perfectionism
EXCELLENCE-K	: Self-Focused Perfectionism
EXCELLENCE-S	: Socially Oriented Perfectionism
HMDPS	: Hewitt Multidimensional Perfectionism Scale
RERS	: Rosenberg Ego Respect Scale
SD	: standard deviation
SPSS	: Statistical Package for the Social Sciences
STAI	: Spielberg State-Trait Anxiety Inventory

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The Relationship Of Free ß-hCG, PAPP-A, AFP, ß-hCG, UE3 In Pregnancy With Fac, 50 Gram Glucose Screening Test And Birth Weight

Gebelikte Serbest ß-hCG, PAPP-A, AFP, ß-hCG, UE3'in AKŞ, 50 Gram Glukoz Tarama Testi Ve Bebek Doğum Ağırlığı İle İlişkisi

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Abstract

Objective: It is possible to improve the quality of health and care and to minimize high-cost medical expenses by closely monitoring the complications in infants born with abnormal fetal birth weights. Within the scope of this research, we aimed to elucidate the relationship between first and second-trimester screening tests plasma proteins and 50 g glucose tolerance test values used in gestational diabetes screening with estimated birth weight.
Method: A total of 831 cases with regular antenatal follow-ups in Ankara Atatürk Training and Research Hospital, Gynecology, and Obstetrics Clinic were enrolled. The first- trimester fetal aneuploidy screening determined PAPP-A and free-β-hCG values. The second- trimester triple test determined Alpha-feto protein, hCG, and unconjugated estriol values. Fasting blood glucose was measured at the first visit, and a 50 g oral glucose tolerance test (OGTT) was performed between 24 – 28 weeks of gestation. Pregnancies continued without complications and who gave birth at term (gestational age 37+0 weeks) were included in the study.
Results: When the relationship between the hormonal values used in the first and second-trimester aneuploidy screening and the 50 gr OGTT (mg/dl) values are examined, no correlation between free-beta-hCG and 50 g OGTT (mg/dl) (r= -0.055, p= 0.128). Maternal fasting blood glucose levels (r= -0.055, p= 0.131) did not reveal any relationship with first and second-trimester aneuploidy screening. PAPP-A (r= - 0.011, p= 0.765), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340). (Figure 14), and hCG values (r= -0.051, p= 0.164), also did not present correlation with maternal fasting blood glucose levels.
Conclusion: According to the results of our study, no relationship was found between the hormones used in the first trimester (PAPP-A and free-beta-hCG) and second-trimester (AFP, hCG, and uE3) aneuploidy screening and 50 g OGTT, maternal plasma blood glucose level and birth weight.

Keywords: Gestational Diabetes Mellitus, Abnormal Birth Weight, Trimester, Pregnancy-Associated Plasma Protein-A (PAPP-A), Unconjugated Estriol (uE3).

Özet

Amaç: Anormal fetal doğum ağırlığı ile doğan bebeklerde komplikasyonların yakından izlenmesi ile sağlık ve bakım kalitesinin artırılması ve yüksek maliyetli tıbbi harcamaların en aza indirilmesi mümkündür. Bu araştırma kapsamında, gestasyonel diyabet taramasında kullanılan 50 g glukoz tolerans testi değerleri ile tahmini doğum ağırlığı ile birinci ve ikinci trimester tarama testleri plazma proteinleri arasındaki ilişkiyi ortaya koymayı amaçladık.
Yöntem: Ankara Atatürk Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'nde düzenli antenatal takipleri olan toplam 831 olgu çalışmaya alındı. Birinci trimester fetal anöploidi taraması PAPP-A ve serbest-β-hCG değerlerini belirledi. İkinci trimester üçlü testi, Alfa-feto protein, hCG ve konjuge olmayan estriol değerlerini belirledi. İlk vizitte açlık kan şekeri ölçüldü ve 24-28. gebelik haftaları arasında 50 gr oral glukoz

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tolerans testi (OGTT) yapıldı. Gebelikleri komplikasyonsuz devam eden ve miadında (gebelik yaşı 37+0 hafta) doğum yapanlar çalışmaya dahil edildi.
Bulgular: Birinci ve ikinci trimester anöploidi taramasında kullanılan hormon değerleri ile 50 gr OGTT (mg/dl) değerleri arasındaki ilişki incelendiğinde, serbest-beta-hCG ile 50 gr OGTT (mg/dl) arasında korelasyon saptanmadı (r= -0.055, p= 0.128). Maternal açlık kan şekeri düzeyleri (r= -0.055, p= 0.131) birinci ve ikinci trimester anöploidi taraması ile herhangi bir ilişki göstermedi. PAPP-A (r= - 0.011, p= 0.765), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340) ve hCG değerleri (r= -0.051, p= 0.164) de anne açlık kan şekeri seviyeleri ile korelasyon göstermedi.
Sonuç: Çalışmamızın sonuçlarına göre birinci trimesterde kullanılan hormonlar (PAPP-A ve serbest-beta-hCG) ve ikinci trimesterde (AFP, hCG ve uE3)anöploidi taraması ile 50 g OGTT, maternal plazma kan şekeri düzeyi ve doğum ağırlığı arasında ilişki bulunmadı.

Anahtar Kelimeler: Gestasyonel Diabetesmellitus, Anormal Doğum Ağırlığı, Trimester, Gebelikle İlişkili Plazma Protein-A (PAPP-A), Konjuge Olmayan Estriol (uE3).

INTRODUCTION

In 2-3% of pregnancies, major congenital anomalies are identified during pregnancy or immediately after delivery. These anomalies are responsible for 20% of infant deaths and have become the most common cause. Prenatal diagnosis; It is the science that identifies malformations, birth defects, chromosomal abnormalities, and other genetic syndromes in the fetus. The aim of prenatal diagnosis is to improve counseling services and outcomes by providing accurate information about short and long-term prognosis, risk of recurrence, and potential treatment (1). In recent years, thanks to the new developments in prenatal diagnosis methods, detecting many anomalies in the early period has become possible (2).

Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 3-4% of all pregnant women. 90% of this is gestational diabetes mellitus. Babies of mothers with GDM are at risk of developing obesity, impaired glucose tolerance, and diabetes at an early age (2, 3).

The biological function of pregnancy-associated plasma protein-A (PAPP-A), one of the four proteins detected in high concentration in pregnant blood in 1974, was unknown. In 1992, Wald suggested that PAPP-A is lower than normal in pregnancies with Down syndrome (DS) in the first trimester, and it has been used in routine medical practice as part of first-trimester screening tests since the second half of the 1990s. In 1999, it was reported that PAPP-A is the IGF-dependent IGFBP-4 protease isolated from human fibroblast culture medium (3). In the 2000s, it was understood that PAPP-A plays a critical role in growth and development and is involved in many physiological and pathophysiological processes by regulating local IGF concentration (4).

Similar to PAPP-A, various biomarkers have been identified and integrated into screening tests for anomaly screening. In the first trimester (11 – 14 weeks), free beta-human chorionic gonadotropin (f-ßhCG) and PAPP-A biochemical parameters and fetal nuchal translucency (NT) measurements have become almost the standard method to determine the risk of trisomy 21, 13 and 18. Thus, it is possible to detect the risk of trisomy in the early period with an accuracy of approximately 85-90% (5). One of the screening tests used in the second trimester is the triple screening test; its reliability is 61-70% (1). It is used in the determination of trisomy 21, 18, 13, and neural tube defects by looking at alfa-feto protein (AFP), uE3, and ßhCG in maternal serum (6).

As the function of these proteins, which are used in anomaly screening tests in recent years, is understood, various studies have been carried out in order to use them for the pre-detection of

some conditions (preeclampsia, IUGR, gestational diabetes, macrosomia, preterm birth, polyhydramnios, fetal sex, etc.). Placental proteins include ß-hCG, PAPP-A, AFP, uE3, and Inhibin-A. The results of the pregnancy values of these proteins I mentioned in terms of preeclampsia, fetal sex, and gestational diabetes were compared in various studies, and it was evaluated whether there was a relationship between them (7).

Gestational diabetes mellitus (GDM) is a glucose intolerance disorder that first appears during pregnancy or is diagnosed during pregnancy. GDM rate in all pregnancies is 1 – 14%. The main mechanism in the pathogenesis of gestational diabetes is a maximum of 24 – 28. Insulin resistance is triggered by placental hormones and autoimmune origin proteins (HLA-DR 2, 3, 4 antigens) and the inability to meet the increased insulin requirement by maternal pancreatic beta cells. Hormones that increase insulin resistance are human placental lactogen (HPL), growth hormone (GH), progesterone, corticotropin-releasing hormone (CRH), cortisol, and prolactin (PRL) (8).

It is possible to improve the quality of health and care and to minimize high-cost medical expenses by closely monitoring the complications that may occur in infants born with abnormal fetal birth weights (9). Within the scope of this research, we aimed to elucidate the relationship between first and second-trimester screening tests plasma proteins and 50 g glucose tolerance test values used in gestational diabetes screening with estimated birth weight.

METHOD

A total of 831 cases with regular antenatal follow-ups in Ankara Atatürk Training and Research Hospital, Gynecology, and Obstetrics Clinic were enrolled. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution.

The first-trimester fetal aneuploidy screening determined PAPP-A and free-β-hCG values. The second-trimester triple test determined Alpha-feto protein, hCG, and unconjugated estriol values. Fasting blood glucose was measured at the first visit, and a 50 g oral glucose tolerance test (OGTT) was performed between 24 – 28 weeks of gestation. Among these cases, 759 cases whose pregnancies continued without complications and who gave birth at term (gestational age 37+0 weeks) were included in the study.

The descriptive data of the pregnant women, age, gravida, and parity values, birth weeks and birth weights (g), and maternal plasma PAPP-A, free-beta-hCG, alpha-feto protein, hCG, and unconjugated estriol values were recorded as MoM. Fasting plasma glucose (FPG) and 50 g OGTT values were calculated as mg/dl and recorded. It was investigated whether there is a relationship between maternal plasma hormone values and FGW, 50 gr OGTT values, and birth weights and hormone values.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T–test" was used for two groups, and the "Pearson Chi-Square Test" was used for the comparison of categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

The mean age of 759 cases was 26.8±4.7 (range 16 – 41). The gravida was 2.2±1.2 (range 1 – 10), and parity was 0.9±0.8 (range 0 – 5). The mean FPG value was 83.6±11.3 (range 49 – 136) mg/dl, 50 g OGTT was 117.0±28.3 (range 53 –224) mg/dl, and birth weight was 3350±449 g. When the relationship between the hormonal values used in the first and second-trimester aneuploidy screening and the 50 gr OGTT (mg/dl) values are examined, no correlation between free-beta-hCG and 50 g OGTT (mg/dl) (r= -0.055, p= 0.128).

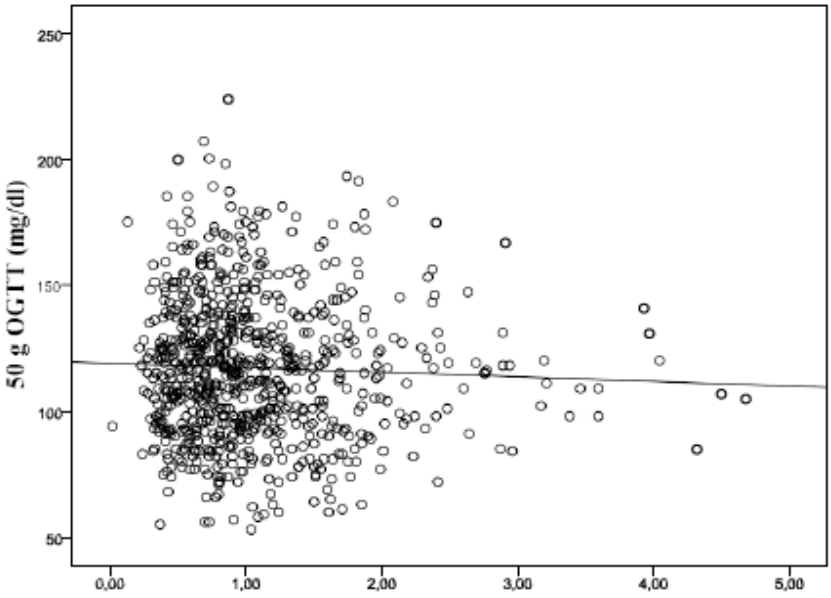

Figure 1. Correlation Of PAPP-A (MoM) With 50 g OGTT (mg/dl)

No correlation was found between PAPP-A and 50 g OGTT (mg/dl) (r= -0.041, p= 0.262) (Figure 2) and between AFP (MoM) and 50 g OGTT (mg/dl) (r= 0.022, p= 0.554) (Figure 1). Additionally, we could not achieve a correlation between uE3 (MoM) and 50 g OGTT (mg/dl) (r= - 0.022, p= 0.540), and between hCG (MoM) and 50 g OGTT (mg/dl) (r= 0.031, p= 0.399).

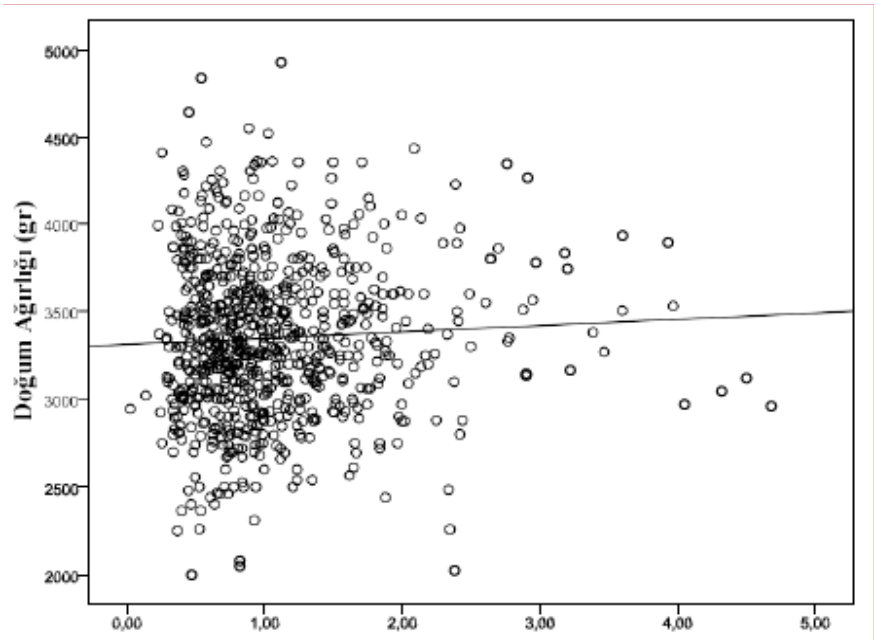

Figure 2. Correlation Of PAPP-A With Birth Weight (g)

When the relationship between hormonal values and birth weight (g) values in the first and second-trimester aneuploidy screening was examined, there was no correlation between free-beta-hCG (r=-0.022, p= 0.542), PAPP-A (r= -0.051, p= 0.159) (Figure 2), AFP (r= 0.012, p= 0.744), uE3 (r= 0.069, p= 0.056), hCG (r= -0.010, p= 0.790) and birth weight.

Maternal fasting blood glucose levels (r= -0.055, p= 0.131), did not reveal any relationship with first and second-trimester aneuploidy screening.

PAPP-A (r= - 0.011, p= 0.765) (Figure 3), AFP (r= -0.033, p= 0.369), uE3 (r= 0.035, p= 0.340) (Figure 3), and hCG values (r= -0.051, p= 0.164), also did not present correlation with maternal fasting blood glucose levels.

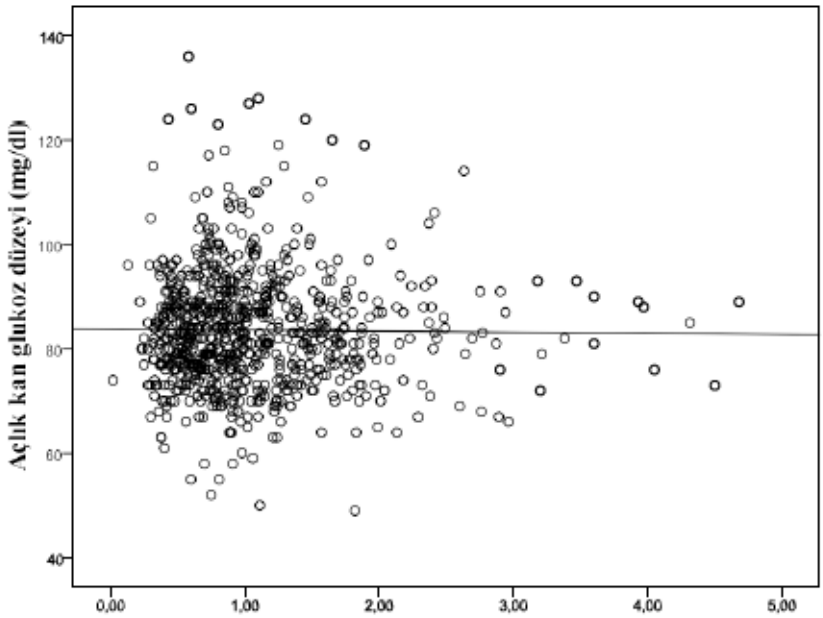

Figure 3. Correlation Of PAPP-A With Maternal Fasting Blood Glucose Level

DISCUSSION

Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 3-4% of all pregnant women. 90% of this is gestational diabetes mellitus. Babies of mothers with GDM are at risk of developing obesity, impaired glucose tolerance, and diabetes. It is a metabolic disorder that can cause morbidity and mortality ranging from congenital malformations to in-utero death in the baby, from hypoglycemia in the mother to diabetic ketoacidosis, increased retinopathy, and nephropathy when adequate glycemic control is not achieved (10).

The main mechanism in the pathogenesis of gestational diabetes is insulin resistance triggered by placental hormones and proteins of autoimmune origin (HLA-DR 2,3,4 antigens) and the inability to meet the increased insulin requirement by maternal pancreatic beta cells. Hormones that increase insulin resistance are HPL, growth hormone, progesterone, CRH, cortisol, and PRL (11). HPL is the main hormone responsible for insulin resistance in pregnancy, and it achieves this effect by decreasing the affinity of insulin for its receptor, although it is not certain. It also reduces the use of carbohydrates for energy by increasing lipolysis in adipose tissue. Thus, glucose and amino acids are stored for the fetus (12). As a result of increasing insulin resistance during pregnancy, the amount of insulin secreted from the pancreas to provide maternal euglycemia increases more than two times compared to non-pregnant women. This situation can be tolerated physiologically in normal pregnant women, it cannot be compensated

during pregnancy in diabetic women and many women who were not known to have diabetes before, and the balance of carbohydrate metabolism is disturbed (13).

It shows its hCG activity through the LH/hCG receptor, and its major function is to provide progesterone production (14). Increased progesterone with hCG contributes to insulin resistance. In previous studies, it was reported that hCG-ß promotes growth. With this effect, it can be thought that it can directly contribute to birth weight. Another effect of the placenta is the prolongation of the half-life of hCG, a glycoprotein carrying a carbohydrate side chain (15).

Compared to normoglycemic individuals, a history of macrosomic infant delivery is three times more common in diabetics. These babies have excessive fat accumulation on the shoulders and trunks. The main factor in the development of macrosomia is fetal hyperinsulinemia developing in response to maternal hyperglycemia. About 80% of maternal glucose levels also occur in the fetus. Thus, fetuses of hyperglycemic mothers synthesize more insulin. In the fetus, tissues sensitive to insulin, such as the liver, adipose tissue, muscle tissue, heart, adrenal glands, and pancreas, undergo hypertrophy and hyperplasia. The same change is not seen in the length of the brain, kidneys, and femur (16). Similarly, maternal amino acid use decreases as a result of insulin resistance and hypoinsulinemic state in diabetics, and fetal development accelerates as a result of increased circulating amino acids passing to the fetus and stimulating insulin secretion. GDM, which may develop with the effect of these hormonal stimuli, can be detected by evaluating with 50 g OGTT performed between 24 – 28 weeks (17).

Insulin-like growth factors (IGFs), which stimulate cell proliferation and differentiation, exert the most important effect on fetal growth. Serum IGF levels in the prenatal period are lower than in the postnatal period, increase during pregnancy and show a positive correlation with birth weight. Placental somatotropins (placental lactogens) stimulate the synthesis of IGF-I and IGF-II (18).

PAPP-A is secreted by trophoblasts in the placenta; It has been found to be IGF-dependent IGFBP-4 protease. IGFBP-4 has a high affinity for IGFs and prevents cell growth by binding IGF and preventing them from interacting with IGF-I receptors. It is also an inhibitor of IGFBP. PAPP-A severely reduces its affinity for IGFs by cleaving IGFBP-4 in the middle. This mechanism may account for the increase in birth weight at high PAPP-A levels (19). The study of Savvidou and Nicolaides et al. reported the relationship between first-trimester maternal serum f-βhCG and PAPP-A levels and gestational diabetes was examined, and no correlation was found between them. As a result, it was found that low βhCG levels in the second trimester were associated with gestational diabetes (20). Our study showed a difference between first-trimester f-βhCG and OGTT.

While no significant relationship was found, no significant relationship was found between second-trimester βhCG values and FPG and OGTT. Significant results can be obtained in studies performed by setting a threshold value for second trimester βhCG values (above 0.81 MoM). The relationship between serum PAPP-A values and gestational diabetes revealed that the relationship between low PAPP-A values and gestational diabetes was significant (21). Another stated that low PAPP-A levels in the first trimester were associated with possible gestational diabetes (22).

Birth weight is directly related to maternal race, age, body mass index, number of births, smoking, and pre-pregnancy DM in relation to the gestational period. The large size of the fetus complicates the delivery and puts the mother at risk. Identifying the factors that control fetal growth will be beneficial in understanding the pathophysiology of the disease, preventing complications, and treatment. In the past, it was argued that the variability observed in fetal

growth occurred mainly in the second half of pregnancy when antenatal care was given (23). Later studies have reported that embryos and fetuses smaller than expected in the first trimester are more prone to complications such as growth retardation and premature birth (24). In published studies, a significant relationship was found between birth weight percentiles and adjusted PAPP-A values. Habayeb et al. showed a positive correlation between first-trimester PAPP-A MoM values and birth weight (25). Pregnancies with increased PAPP-A MoM values were observed to have higher birth weights. A study also states a positive correlation between PAPP-A and birth weight in complicated pregnancies with maternal diabetes (26). In our study, no significant relationship was found between birth weight and PAPP-A value; Although there was no difference in material method with studies with positive correlation, it was mentioned in one study that a cutoff value was used for PAPP-A MoM (<0.55 MoM).

Bader et al. reported a significant negative correlation between AFP and birth weight (27). However, babies born under 2500 g were not included in their study. In other similar studies, it has been determined that high maternal serum AFP levels may be associated with the birth of a baby with intrauterine growth retardation (28, 29). In our study, no relationship was found between AFP and birth weight. The studies with positive correlations did not include maternal systemic disease, drug use, genetic reasons affecting growth, GDM, multiple pregnancies, and pregnancies without follow-up. Despite this, studies also show no relationship between maternal serum AFP and birth weight at any gestational week (30). In this study, AFP was measured in umbilical cord blood, and an inverse relationship was found between birth weight and birth weight.

We could not find a relationship between our parameters and birth weight in our study, despite the significant results previously determined, maybe the inclusion of a heterogeneous patient population.

CONCLUSION

According to the results of our study, no relationship was found between the hormones used in the first trimester (PAPP-A and free-beta-hCG) and second-trimester (AFP, hCG, and uE3) aneuploidy screening and 50 g OGTT, maternal plasma blood glucose level and birth weight.

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Competing interests: The authors declare that they have no competing interests.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. As this was a retrospective research no informed consent has been obtained from participants.

Abbreviations

AFP : Alfa-feto protein
CRH : Corticotropin-releasing hormone
DS : Down Syndrome
FPG : Fasting plasma glucose

f-ßhCG : Free beta-human chorionic gonadotropin
GDM : Gestational diabetes melltus
GH : Growth hormone
hCG : Human chorionic gonadotropin
HLA : Human leucocyte antigen
HPL : Human placental lactogen
IGFs : Insulin-like growth factors
IUGR : Intra-uterine growth retardation
NT : Nuchal translucency
OGTT : Oral glucose tolerance test
PAPP – A : Pregnancy-associated plasma protein-A
PRL : Prolactin
SPSS : Statistical Package for the Social Sciences
uE3 : Unconjugated estriol

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The Effect of Breastfeeding Duration on Executive and Cognitive Functions at Healthy School Age Children

Anne Sütü Alım Süresinin Okul Çağı Çocuklarında Yürütücü İşlevlere ve Bilişsel Düzeye Etkisi

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Abstract

Breast milk is a natural food and contains all the nutrients the baby needs for healthy growth. The last trimester of the intrauterine period and the first 2 years of life are the periods which brain development peaks. Docosahexaenoic Acid (DHA) and Arachidonic Acid (AA) accumulate in the membranes of brain cells during these periods when brain development peaks. DHA is particularly involved in the myelination process of the frontal lobe. In addition to DHA and AA, breast milk also contains cholesterol, sphingomyelin, phosphoditylcholine, which are necessary for myelin synthesis. The aim of this study is to evaluate the effect of duration of exclusively breastfeeding on cognitive level and executive functions in school–aged children with no psychiatric complaint. A total of 71 children aged 8-13 years without any psychiatric diagnosis constituted the study group. According to the duration of receiving only breast milk, they were separated into 2 groups as those who receive only breast milk for less than 6 months and those who receive breast milk for 6 months or more. The children's executive functions were assessed with Stroop Test and Wisconsin Card Sorting Test (WCST) respectively. After the executive function tests, Verbal subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) including General Knowledge and Vocabulary and Performance subtests of the WISC-R including Picture Completion, Picture Arrangement were applied to the children. In our study, the parent form of the Strengths and Difficulties Questionnaire (SDQ) was used to screen the behavioral and emotional problems of children. Standard scores of WISC-R (total and subtests), Stroop Test and WCST were similar for both groups ($p>0.05$). In our study, we found that the duration of exclusively breastfeeding did not have an effect on the cognitive level and executive functions of the child.

Keywords: Breastfeeding, Executive Functions, Cognition, Intelligence, Child and Adolescent.

Özet

Anne sütü bebeğin sağlıklı büyümesi için ihtiyaç duyduğu tüm besinleri içeren doğal bir besindir. İntrauterin son üç ay ve yaşamın ilk 2 yılı beyin gelişiminin zirve yaptığı dönemlerdir. Dokosaheksaenoik Asit (DHA) ve Araşidonik Asit (AA) beyin gelişiminin zirve yaptığı bu dönemlerde beyin hücrelerinin zarlarında birikir. DHA, özellikle frontal lobun miyelinasyon sürecinde yer alır. Anne sütünde DHA ve AA'nın yanı sıra miyelin sentezi için gerekli olan kolesterol, sfingomyelin, fosfoditilkolin de bulunmaktadır. Bu çalışmanın amacı, psikiyatrik yakınması olmayan okul çağındaki çocuklarda sadece anne sütü ile beslenme süresinin bilişsel düzey ve yürütücü işlevler üzerine etkisini değerlendirmektir. Çalışma grubunu 8-13 yaşları arasında herhangi bir psikiyatrik tanısı olmayan toplam 71 çocuk oluşturdu. Anne sütü alma sürelerine göre 6 aydan az sadece anne sütü alanlar ile 6 ay ve üzerinde anne sütü alanlar olarak 2 gruba ayrıldı. Çocukların yürütücü işlevleri sırasıyla Stroop Testi ve Wisconsin Kart Eşleme Testi (WKET) ile değerlendirildi. Yürütücü işlev testleri sonrasında çocuklara WISC-R'nin Genel Bilgi ve Sözcük dağarcığını içeren Sözel alt testleri ve WISC-R'nin Resim Tamamlama, Resim Düzenleme gibi Performans alt testleri uygulanmıştır. Çalışmamızda çocukların duygusal ve davranışsal problemlerini taramak için Güçler ve Güçlükler Anketi'nin (GGA) ebeveyn formu kullanılmıştır. Stroop testi, WKET ve WISC-R(toplam ve alt testler) standart puanları her iki grup için benzerdi ($p>0.05$). Çalışmamızda sadece anne sütü ile beslenme süresinin çocuğun bilişsel düzeyi ve yürütücü işlevleri üzerinde etkisi olmadığını saptadık.

Anahtar Kelimeler: Anne Sütü, Yürütücü İşlevler, Biliş, Zekâ, Çocuk ve Ergen.

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INTRODUCTION

The World Health Organization suggest that only breastfed for the first 6 months from birth, start complementary foods after 6 months, and continue breastfeeding until the age of 2 years (1). The positive effects of breastfeeding on maternal and infant health are well known. While breastfeeding protects the mother against breast cancer, it also protects the baby against the diseases. Breast milk is a natural food and contains all the nutrients the baby needs for healthy growth (2). Polyunsaturated fatty acids such as Docosahexaenoic Acid (DHA) and Arachidonic Acid (AA) in breast milk are a significant effect on the neurodevelopmental process. The last trimester of the intrauterine period and the first 2 years of life are the periods which brain development peaks (3). DHA and AA accumulate in the membranes of brain cells during these periods when brain development peaks (4). DHA is particularly involved in the myelination process of the frontal lobe. Disruption of myelenization because of consuming nutrition deficient in DHA causes deterioration of cognitive functions (5). In addition to DHA and AA, breast milk also contains cholesterol, sphingomyelin, phosphoditylcholine, which are necessary for myelin synthesis (5). The increase in white matter volume in adolescents who were breastfed as infants is evidence that the content of breast milk is important in the formation and development of myelin (6,7). Exclusively breastfeeding is associated with earlier development of the frontal and temporal lobe white matter, corticospinal tract, periphery of the internal capsule, superior longitudinal fascicle, and superior occipito-frontal fascicle (8). These regions and pathways are related to higher-order cognition such as language, executive functions, planning, social emotional functioning, and language domains (9,10). Skin-to-skin contact, verbal communication, and stimuli are more common in breastfed babies compared to bottle feeding. It has been reported that the contribution of breastfeeding to the cognitive development of the child is not only related to breastfeeding, but also with other positive parameters such as the intelligence level, education, socioeconomic level of the mother and father (11).

Although many benefits of breast milk during infancy are known, its effects in late childhood are not well known. While the effect of breastfeeding on Intelligence Quotient (IQ) has been examined in many studies, studies investigating the effect on executive functions are limited. Executive functions affect academic achievement and social functioning in later ages.

The purpose of our study is to assess the effect of exclusive breastfeeding duration on cognitive level and executive functions in school-age children without psychiatric complaints.

METHODS

Participants

The ethics committee approval of the study was given by the ethics committee of Marmara University with the protocol number of 09.2014.0190. After obtaining the approval of the ethics committee, with the permission of the Provincial Directorate of National Education the 5th, 6th and 7th grades of the school were determined by random sampling. A total of 300 children in these classes were screened with the Child Behavior Checklist (CBCL). Children with low symptom severity on the CBCL scale and their parents were invited to Marmara University Pendik Training and Research Hospital. The children were assessed clinically by child and adolescent psychiatrist. A total of 71 children aged 8-13 years without any diagnosis constituted the study group. Children with an intelligence level of less than 80 (WISC -R verbal, performance and/or total score<80), any psychiatric disorder, a history of Autism Spectrum Disorders, chronic and serious medical illness and seizure-like neurological disorder were excluded from the study.

In the sociodemographic information form we asked the families that duration of exclusive breastfeeding without feeding additional food or formula. The study group divided into two according to the information received from the families. The first group consisted of children who were exclusively breastfed for 6 months or more. The second group consisted of children who were exclusively breastfed for less than 6 months.

Measurements

The children's executive functions were assessed with Stroop Test and Wisconsin Card Sorting Test (WCST) respectively. After the executive function tests, Verbal subtests of the WISC-R including General Knowledge and Vocabulary and Performance subtests of the WISC-R including Picture Completion, Picture Arrangement were applied to the children. In our study, the parent form of the Strengths and Difficulties Questionnaire (SDQ) was used to screen the behavioral and emotional problems of children. After the tests applied to the child and the clinical interview were completed, the forms filled by the parents were reviewed together with the child and adolescent psychiatrist and the parts that the parents could not understand were evaluated. Clinical Interviews lasted approximately 1.5 hours for each participant and were completed in a single session. The tools we used in our study were briefly explained below.

Stroop Test

The Stroop test was first developed by Stroop in 1935 (12). The adaptation study of the test to the 6-11 age group was carried out by Kılıç and Koçkar in 2002, and the validity and reliability study for adults in our country was carried out by Karakaş in 1999(13,14). The Stroop test measures ability to change response, information processing speed, and especially selective attention.

Wisconsin Card Sorting Test (WCST)

It was developed by Berg in 1948 in order to evaluate abstraction and conceptualization skills (15). In our country, standardization studies were carried out by Karakaş (16). WCST is associated with features such as attention, feature identification, perseveration, working memory, executive functions, conceptualization, and abstract thinking.

Wechsler Intelligence Scale for Children-Revised (WISC-R)

It is a scale developed by David Wechsler to evaluate the general mental capacity of children aged 5-15 years (17). Standardization studies in our country were made by Savaşır and Şahin and WISC-R scale was adapted to Turkish culture (18).

Strengths and Difficulties Questionnaire (SDQ)

SDQ was developed by Robert Goodman in 1997 (19). The Turkish validity and reliability study was conducted by Güvenir et al. in 2008 (20). SDQ is used to screen for the behavioral and emotional problems in children and young people.

RESULTS

A total of 71 children between 8 and 13 year ages were evaluated in our study. All of the cases participating in our study consisted of healthy children who did not have any psychiatric

complaints and were not diagnosed with any disorder with the semi-structured interview. Our groups were divided into two based on the retrospective information given by the mother in terms of duration of exclusive breastfeeding. 51% (n= 36) of the cases were exclusively breastfed for 6 months or more, and 49% (n=35) of cases were exclusively breastfed for less than 6 months. Mean age and gender distributions of two the groups were similar. There was no statistically significant difference between the groups in the term of developmental stages such as saying the first words, making the first sentence, walking and starting toilet training.

The duration of bottle use in exclusively breastfed less than 6 months was longer than the other group and there was a statistically limited difference (p=0.05). Duration of pacifier use were similar in both groups.

There was no statistically significant difference between the two groups in terms of medical and mental problems of the mothers during pregnancy, drug using and/or smoking, exposure to radioactive rays and trauma in perinatal period. Parents' ages, education levels and socioeconomic levels were similar in both groups.

Attention deficit and hyperactivity, behavioral problems, emotional problems, peer problems, social behavior subtest and total difficulty scores of the SDQ were compared separately, the mean score of those who received only breastmilk for less than 6 months was higher than the other group, but it did not reach the level of statistical significance (p> 0.05). (Table 1)

Table 1. Strengths and Difficulties Questionnaire (SDQ) Parent Form, Comparative Subtest Scores

SDQ Subscales	Exclusively breastfed for less than 6 months		Exclusively breastfed for 6 months or more		
	Mean±sd	Median (min-max)	Mean±sd	Median (min-max)	z and p values
Hyperactivity/ Inattention	4.23±1.88	4 (0-9)	3.94±1.51	4 (1-7)	z=-0.598 p=0.550
Conduct Problems	1.43±1.79	1 (0-9)	1.11±1.14	1 (0-5)	z=-0.462 p=0.644
Emotional Problems	2.26±2.44	1 (0-8)	1.67±1.64	1 (0-7)	z=-0.559 p=0.576
Peer Relationship Problems	3.09±2.23	3 (0-8)	2.72±1.5	3 (0-6)	z=-0.432 p=0.665
Prosocial Behaviour	8.29±1.47	8 (4-10)	8.14±2.29	8 (4-15)	z=-0.231 p=0.818
Total Difficulty Points	10.49±6.43	9 (0-35)	9.44±3.81	9 (2-16)	z=-0.345 p=0.568

Mann-Whitney U Test.

Standard scores of Verbal subtests of the WISC-R including General Knowledge and Vocabulary and Performance subtests of the WISC-R including Picture Completion, Picture Arrangement were similar for both groups (p>0.05). (Table 2)

Table 2. WISC-R Subtest Standard Scores

	Exclusively breastfed for less than 6 months		Exclusively breastfed for 6 months or more		
	Mean±sd	Median (min-max)	Mean±sd	Median (min-max)	z and p values
General Knowledge	10.37±2.51	10 (4-15)	9.89±2.14	10 (6-15)	z=-1.131 p=0.258
Vocabulary	11.77±1.88	12 (9-17)	11.28±1.88	11 (7-14)	z=-0.706 p=0.480
Picture Completion	12.03±2.06	12 (9-16)	12.08±1.93	12 (7-16)	z=-0.408 p=0.683
Picture Arrangement	10.65±1.68	11 (7-15)	10.75±2.75	11 (7-20)	z=-0.169 p=0.866

Mann-Whitney U Test.

When all of the participants (n=71) were evaluated together without being divided into two groups, it was determined that total and exclusive breastfeeding duration were not related to the intelligence test results. (Table 3)

Table 3. The Relationship Between Total And Exclusive Breastfeeding Duration And WISC-R Test Results

		Exclusively Breastfeeding	Total Breastfeeding
WISC-R Verbal	r	-0.044	-0.14
	p	0.714	0.244
	n	71	71
WISC-R Performance	r	-0.121	-0.137
	p	0.313	0.253
	n	71	71
WISC-R Total	r	-0.091	-0.176
	p	0.448	0.143
	n	71	71

Spearman's rho correlation analysis

When the Stroop test results were compared, no statistically significant difference was found between the two groups. (Table 4)

Table 4. Stroop Test TBAG Version Comparative Results

Stroop Test TBAG Form		Exclusively breastfed for less than 6 months		Exclusively breastfed for 6 months or more		
		Mean±sd	Median (min-max)	Mean±sd	Median (min-max)	z and p values
Section 1	Time	10±2.5	10 (6-19)	10.64±2.81	10 (7-18)	z=-0.890 p=0.374
	Fault	0.00	0 (0-0)	0.03±0.17	0 (0-1)	z=-0.986 p=0.324
	Correction	0.11±0.4	0 (0-0)	0.00	0 (0-0)	z=-1.782 p=0.075
Section 2	Time	10.74±5.68	10 (2-40)	11.58±3.33	10,5 (8-20)	z=-1.671 p=0.095
	Fault	0.06±0.34	0 (0-2)	0.00	0 (0-0)	z=-1.014 p=0.310
	Correction	0.03±0.17	0 (0-1)	0.08±0.28	0 (0-1)	z=-0.993 p=0.320
Section 3	Time	15.34±4.43	15 (8-28)	17.67±6.52	16 (11-41)	z=-1.495 p=0.135
	Fault	0.09±0.37	0 (0-2)	0.08±0.28	0 (0-1)	z=-0.389 p=0.679
	Correction	0.17±0.38	0 (0-1)	0.42±0.69	0 (0-2)	z=-1.491 p=0.136
Section 4	Time	23.14±8.14	23 (8-45)	26.06±12.65	24 (13-82)	z=-0.835 p=0.404
	Fault	0.14±0.69	0 (0-4)	0.06±0.23	0 (0-1)	z=-0.058 p=0.954
	Correction	0.74±0.82	1 (0-3)	1.11±1.33	1 (0-6)	z=-0.982 p=0.326
Section 5	Time	34.03±10.57	34 (12-75)	36.56±18.08	31 (17-115)	z=-0.086 p=0.931
	Fault	0.17±0.45	0 (0-2)	0.47±0.84	0 (0-3)	z=-1.541 p=0.123
	Correction	1.63±1.29	2 (0-4)	2±1.62	2 (0-7)	z=-0.838 p=0.402

Mann-Whitney U Test.

When the WCST results of the 2 groups were compared, we could not find a statistically significant difference. (p>0.05). (Table-5)

Table 5. Wisconsin Card Sorting Test Comparative Results

Wisconsin Card Sorting Test (WCST)	Exclusively breastfed for less than 6 months		Exclusively breastfed for 6 months or more		
	Mean±sd	Median (min-max)	Mean±sd	Median (min-max)	z and p values
WCST2	37.57±19.45	30 (15-94)	41.17±19.28	35 (16-90)	z=-1.358 p=0.174
WCST3	90.43±19.45	98 (34-113)	86.83±19.28	93 (38-112)	z=-1.358 p=0.174
WCST4	5.46±2.41	6 (0-10)	5.03±2.42	5 (1-9)	z=-0.620 p=0.535
WCST5	23.91±22.97	16 (7-113)	25.61±19.77	18.5 (7-106)	z=-1.502 p=0.133
WCST6	20.91±17.05	15 (6-84)	22.67±15.05	17.5 (7-81)	z=-1.497 p=0.134
WCST7	16.66±8.78	15 (5-45)	18.5±9.94	17 (5-52)	z=-1.054 p=0.292
WCST8	16.32±13.32	11.72 (4.66-65.63)	17.71±11.76	13.67 (5.47-63.28)	z=-1.520 p=0.128
WCST9	15.18±6.53	13 (10-32)	15.47±8.81	12 (10-54)	z=-0.873 p=0.382
WCST11	62.812±19.96	70.31 (7.03-85.16)	58.85±20.23	66.8 (12.5-87.5)	z=-1.236 p=0.216
WCST12	2.03±1.69	1 (0-5)	1.94±1.33	2 (0-6)	z=-0.235 p=0.814

Mann-Whitney U Test.

When the relationship between total or exclusively breastfeeding duration and executive functions was evaluated; In the Stroop test, a positive correlation was found between the

duration of exclusive breastfeeding and the time score of the 2nd Section, the total duration of breastfeeding and the time scores of the 1st, 2nd and 4th Sections. (Table 6)

Table 6. The Relationship Between Total And Exclusive Breastfeeding Duration And Stroop Test

STROOP TEST		Stage 1 Time	Stage 2 Time	Stage 3 Time	Stage 4 Time	Stage 5 Time
Exclusively Breastfeeding	r	0.101	0.261	0.204	0.107	0.073
	p	0.402	0.028	0.088	0.376	0.546
	n	71	71	71	71	71
Total Breastfeeding	r	0.31	0.279	0.226	0.327	0.208
	p	0.009	0.018	0.058	0.005	0.081
	n	71	71	71	71	71

Spearman's rho correlation analysis.

In the WCST, no correlation was found between the duration of exclusive breastfeeding in WCST ($p>0.05$). Positive relationship between total breastfeeding time and WCST 2, WCST 5, WCST 6, and WCST 8 results; A negative correlation was found with WCST3 and WCST 11 ($p<0.05$).(Table 7)

Table 7. The Relationship Between Total And Exclusive Breastfeeding Durations And WCST Results

		WCST 2	WCST 3	WCST 4	WCST 5	WCST 6	WCST 7	WCST 8	WCST 9	WCST 11	WCST 12
Exclusively Breastfeeding	r	-0.191	0.191	-0.119	0.223	0.215	0.125	0.217	-0.098	-0.175	0.057
	p	0.11	0.11	0.324	0.062	0.073	0.297	0.069	0.42	0.144	0.635
	n	71	71	71	71	71	71	71	70	71	71
Total Breastfeeding	r	0.328	-0.328	-0.19	0.415	0.41	0.137	0.41	0.023	-0.297	-0.159
	p	0.005	0.005	0.111	0.001	0.001	0.255	0.001	0.85	0.012	0.184
	n	71	71	71	71	71	71	71	70	71	71

Spearman's rho correlation analysis.

DISCUSSION

In our study, 97% of the cases were breastfed for varying periods of time. Breastfeeding is very common in our country. According to Turkey Demographic and Health Survey 2018 data, 98% of all children have been breastfed for a while and 41% of infants younger than 6 months were exclusively breastfed (21). Breastfeeding duration data of our study is compatible with 2018 Turkey data.

In our study, developmental stages of the children were similar regardless of the duration of breastfeeding. In a study investigating the impact of breastfeeding duration on mental development between the ages of 2-3, it was shown that breastfed children were better at developmental stages including language, communication, fine and gross motor compared to non-breastfeed children. In the same study, it was stated that there was a meaningful positive relation between the duration of breastfeeding and motor development (22). The reason why the developmental stages did not differ in our study may be due to the low number of children (n=2) who were not breastfed at all in who take only breast milk for less than 6 months.

In our study, the SDQ was used to examine the effect of exclusively breastfeeding duration on emotional and behavioral problems in children. There was no statistically significant difference between subtest and total difficulty scores of SDQ in both groups. In a comprehensive randomized controlled study in which 13889 children were followed for 6.5 years, it was determined that there was no risk or benefit on the behavior of the child, according to the SDQ filled by both parents and teachers, however, it was stated that these results cannot be generalized on behavioral outcomes that may occur in adolescence and adulthood (23).

We applied the WISC-R test with 4 sub-test. The WISC-R total, performance and verbal scores and the standard scores of the general knowledge, vocabulary, picture completion and picture editing subtests of the two groups were compared to examine the effect of breastfeeding duration on intelligence. In our study, we did not detect a statistically significant difference between the groups.

In a meta-analysis study, a positive correlation was found between breastfeeding and performance intelligence test. Also, the same relationship was shown when the maternal IQ level controlled (24). Mothers who are conscious about breastfeeding create a more stimulating and suitable environment for the cognitive development of their children. The effect of breastfeeding on cognitive functions may be caused not only by nutritional effect but also by the supporting family environment

In a large sample cluster-randomized study followed 13.889 children at age 6.5. Clinicians applied to children IQ test included 4 subtests (vocabulary, similarities, block designs, and matrices). The researchers found that in breastfed group verbal IQ was 7.5 points higher, the performance IQ also 2.9 points and full-scale IQ was 5.9 points higher at the age of 6.5 (25). In the randomized cluster study, which is a 16-year follow-up study examining whether the neurocognitive effect continues in the long term, higher scores were found in the verbal domains in exclusively breastfed (more than 3 months) group but the same effect was not detected in other domains (26). In another a comprehensive prospective study investigating the effect of breastfeeding on intelligence in children by controlling the effect of maternal intelligence and other confounding factors, the intelligence level of children was evaluated at the age of 5 and 14 years, the researchers found that breastfeeding had little or no effect on the child's intelligence. In that study, it was stated that the mother's intelligence level had a greater effect on breastfeeding than the mother's race, education level, age, economic status, smoking, living environment, birth weight of the child. It has been emphasized that the children of mothers with high IQ levels also have a genetically better intelligence level, and there is a positive relationship between the mother's IQ level and breastfeeding initiation and breastfeeding duration (27). The reason of the different results in the studies investigating the effect of breastfeeding on the intelligence of the child may be due to the methodological differences of the studies.

In the literature, while the effect of breastfeeding on intelligence has been investigated in many studies, studies investigating the effect on executive functions are limited. We applied Stroop Test and WCST to children in our study to understand the effect of breastfeeding on executive functions. When we compared the results of Stroop and WCST between the two groups, there was no statistically significant difference. In a large sample study investigating the relation between breastfeeding duration and cognitive performance at the age of 9-10 years showed that breastfeeding duration is not associated with executive functions and memory. In the same study General Ability performance was higher in those breastfed for more than 12 months compared to those who never breastfed (28). In a comprehensive study

examining the effect of breastfeeding duration on the neuropsychological development of healthy children aged 10-12, the neuropsychological performances of less than 6 months breastfed children and 6 months or more breastfed children were compared. It was found that there was no significant or clinically significant relationship between the duration of breastfeeding and neuropsychological test result. It was noted that they performed better only in the language domain (29). In the results of studies, the causal relationship between breastfeeding and neurocognitive functions are uncertain. There is a need for more comprehensive studies to be conducted with different tests and methods investigating the effect of exclusive breastfeeding duration on executive functions.

Limitations

In our study, the duration of breastfeeding was obtained from the retrospective information given by the parents. The fact that the children included in the study were between the ages of 8-13 and this condition raises the possibility of misremembering the information given by the parents about the duration of breastfeeding. Presence of health records regarding the duration of breastfeeding and the prospective design of the study would have eliminated the bias towards recall.

The small sample size of our study makes it difficult to generalize the results. The fact that the cases in our study were taken from a single school and reflect only a part of the society is one of the important limitations. There is a need for comprehensive community-based studies on this subject.

In our study, the number of patients who did not receive any breast milk was only 2. In order to better investigate the effect of breastfeeding on cognitive level and executive functions, a longitudinal evaluations of more non-breastfed cases are required.

The development of executive functions continues throughout childhood and adolescence and varies according to age. In our study, the subjects were in a similar age range, but they were not in the same age range. Evaluation of children in the same age group could provide more specific results.

In our study, the mother's intelligence, which is the most important confounding factor that may have an effect on the child's intelligence and executive functions, was not evaluated. The mother's IQ level may affect genetic transmission to their children’s IQ and duration of breastfeeding.

CONCLUSION

There are limited number of studies in the literature investigating the effect of breastfeeding on executive functions in healthy children. In our study, we found that the duration of breastfeeding had no effect on executive functions and cognitive levels. As a result, prospective studies with large samples are needed to evaluate participants who never breastfed.

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Closure Methods for the Prevention of CSF Fistula in Transsphenoidal Surgery: A Large Study

Transfenoidal Cerrahide BOS Fistülünün Önlenmesine Yönelik Kapatma Yöntemleri: Geniş Kapsamlı Bir Çalışma

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Abstract

Aim and Background: Aim and Background: The primary objective of this extensive series is to conduct a comparative analysis of microscopes and endoscopes and investigate the extent of variability in CSF leakage based on the surgical approach employed, the occurrence of complications during the procedure, the techniques employed for closure, and any postoperative interventions.
Method: A retrospective analysis was conducted on lesions in the sellar region that were surgically treated via the transsphenoidal approach in the Department of Neurosurgery. Microscope, endoscope, or both were used during the approach. The access route used in this study was the transnasal transsphenoidal (TNTS), sublabial, or transcranial+TNTS approach. The repair procedure involved the use of a Surgicel-coated nasal flap, fat graft, or fascia graft and fibrin glue.
Results: The cohort of individuals experiencing CSF leaks exhibited a notably elevated use of endoscopic procedures, while the use of microscopic techniques was relatively few. The incidence of fat graft, nothing, fat+fascia, and the presence of surgicel was rather low in patients presenting with CSF leakage. There was no statistically significant disparity observed in the frequencies of lumber puncture among patients who did not exhibit cerebrospinal fluid leakage. The rates of lumber drainage and meningitis were found to be considerably greater in patients with CSF leak compared to those without ($p<0.001$ for both variables).
Conclusion: It has been suggested that selecting an appropriate closure approach should be based on the intraoperative complications observed during the surgical procedure, to prevent CSF leakage.

Keywords: Transspenoidal Surgery, Endoscope, Cerebrospinal Fluid.

Özet

Giriş ve Amaç: Bu kapsamlı serinin birincil amacı, mikroskop ve endoskopların karşılaştırmalı bir analizini yapmak ve kullanılan cerrahi yaklaşıma dayalı olarak BOS sızıntısındaki değişkenliğin derecesini, prosedür sırasında komplikasyonların ortaya çıkışını, kapama için kullanılan teknikleri araştırmaktır. ve ameliyat sonrası müdahaleler.
Yöntem: Nöroşirürji Anabilim Dalı'nda transsfenoidal yaklaşımla cerrahi olarak tedavi edilen sellar bölgedeki lezyonlar retrospektif olarak incelendi. Yaklaşım sırasında mikroskop, endoskop veya her ikisi birden kullanıldı. Bu çalışmada kullanılan erişim yolu, transnazal transsfenoidal (TNTS), sublabial veya transkranial+TNTS yaklaşımıydı. Onarım prosedürü, surgicel kaplı nasal grefti, yağ grefti ve/veya fasya grefti ve fibrin yapıştırıcı kullanımını içeriyordu.

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Bulgular: Endoskopik prosedürlerde BOS sızıntısı yaşayan bireyler kayda değer bir artış sergilerken, mikroskobik tekniklerin kullanımda nispeten azdı. BOS kaçağı olan hastalarda yağ grefti, hiçbir şey, yağ+fasya ve surgicel varlığı insidansı oldukça düşüktü. Beyin omurilik sıvısı kaçağı göstermeyen hastalar arasında lomber ponksiyon sıklıklarında istatistiksel olarak anlamlı bir eşitsizlik gözlenmedi. BOS kaçağı olan hastalarda olmayanlara göre lumber drenajı ve menenjit oranları anlamlı olarak yüksek bulundu (her iki değişken için $p<0,001$).
Sonuç: Uygun bir kapatma yaklaşımının seçilmesinin, BOS sızıntısını önlemek için cerrahi prosedür sırasında gözlenen intraoperatif komplikasyonlara dayanması gerektiği öne sürülmüştür.

Anahtar Kelimeler: Transspenoidal Cerrahi, Endoskop, Beyin Omurilik Sıvısı.

INTRODUCTION

The adoption of reconstruction techniques is crucial in minimizing the occurrence of cerebrospinal fluid (CSF) leakage subsequent to endoscopic and microscopic transsphenoidal endonasal procedures performed on the skull base. In more than 60% of cases, the surgical intervention of intrasellar lesions might result in significant intraoperative CSF leakage (1). The literature has documented a range of postoperative leak rates for endoscopic pituitary surgery, varying from 1.9% to 10% (2). To reduce this issue, fat grafts may be employed, either with or without the inclusion of fascia or a vascularized septal flap. The implementation of the nasoseptal flap has notably diminished the occurrence of CSF leakage. Various studies have demonstrated that the incidence of CSF leakage following pituitary surgery can be significantly reduced to a range of 0-2.9% with the implementation of a nasoseptal flap for sella reconstruction (3). Nevertheless, it is important to acknowledge that the situation presents certain complications, including nasal pain, severe crusting, and anosmia. The detection or oversight of CSF leakage is possible during the surgical procedure. Following the surgical procedure, the manifestation of any occurrence may arise as a consequence (4). The primary objective of this extensive series is to conduct a comparative analysis of microscopes and endoscopes in their application to the sellar region. Additionally, the study aims to investigate the extent of variability in CSF leakage based on the surgical approach employed, the occurrence of complications during the procedure, the techniques employed for closure, and any postoperative interventions implemented.

METHODS

Patients

A retrospective analysis was conducted on lesions in the sellar region that were surgically treated via the transsphenoidal approach in the Department of Neurosurgery. The study investigated many factors including patient demographics, tumor pathology, type of operation, method of surgical opening, utilization of microscope or endoscope, occurrence of complications during the operation, surgical closure method, and efforts to prevent CSF leaks post-surgery. The analysis focused on examining potential risk factors and preventative approaches associated with postoperative CSF rhinorrhea.

The Identification and Assessment of CSF Fistula

In individuals presenting with suspected postoperative CSF fistula, a positive CSF fistula was determined based on the observation of a noticeable excess of fluid coming from the nasal cavity. The β-2-transferrin test was conducted for diagnostic purposes in cases where suspicion of the condition was present.

The Operation Technique

Microscope, endoscope, or both were used during the approach. The access route used in this study was the transnasal transsphenoidal (TNTS), sublabial, or transcranial+TNTS approach. In the context of opening, otolaryngologists used a septal flap, or the standard opening procedure was conducted.

Techniques for Repairing CSF Leaks

The Valsalva maneuver was executed to ascertain an intraoperative leak's presence. In the case that a CSF leak was identified during the surgical procedure, various solutions were employed to rectify the issue. The repair procedure involved the use of a Surgicel-coated nasal flap, fat graft, or fascia graft. Fibrin glue was added to a subset of the cases. During the post-operative follow-up, external lumbar drainage was maintained for a duration of 2-4 days, or CSF was extracted with lumbar puncture over a period of 2-4 days.

Statistical Analysis

The statistical analysis was conducted using the SPSS 15.0 for Windows software application. The analysis includes descriptive statistics for both categorical and numerical variables. For category variables, the number and percentage are reported. The mean, standard deviation, median, minimum, and maximum values are provided for numerical variables. The rates within the categories were subjected to statistical analysis using the Chi-Square Test. The alpha significance level was deemed statistically significant at a p-value of less than 0.05.

RESULTS

Out of the total sample size of 54 patients, 30 individuals (55.5%) were women, whereas 24 individuals (44.4%) were men. The age distribution of the patients in the study spanned from 5 to 85 years, with a calculated average age of 48. The surgical procedure known as TNTS surgery was conducted on 47 patients, accounting for 87.0% of the sample. Among the remaining patients, 5 individuals (9.2%) underwent a second opening of the TNTS procedure, while 2 patients (3.7%) received a sublabial intervention. The prevalence of apoplexy was 5.5%. Most instances, specifically 51 out of 54 (94,4%), were initiated using a standard opening technique. However, in a minority of cases, precisely 3 out of 54 (5,6%), an alternative approach, including creating a nasal flap, was employed. A microscope was used in 75.9% of the cases, but in 22,2% of the cases, both an endoscope and a microscope were employed simultaneously. In the remaining 1 cases, only the endoscope was employed. Most of the pathological samples consisted of pituitary adenomas, specifically 33 cases (61.1%). During the surgical procedure, 40.7% of CSF was not visually detected, whereas 7.4% of thin arachnoid membranes were detected (Table 1).

The nasal flap rate in individuals with CSF leak was considerably higher than those without CSF leak ($p<0.001$). Statistically significant differences were seen in the frequencies of microscope/endoscope utilization, problems during surgery, and closure of patients without CSF leak ($p<0.001$, $p=0.009$, $p<0.001$, respectively). The cohort of individuals experiencing CSF leaks exhibited a notably elevated use of endoscopic procedures, while the use of microscopic techniques was relatively few. There was no statistically significant disparity observed in the frequencies of lumber puncture among patients who did not exhibit cerebrospinal fluid leakage (Table 2).

Table 1. Summary of clinical characteristics

Age Mean±SD (Min-Max)		**48,9±18,4 (5-85)**	
		n	**%**
Gender	Female	30	55,5
	Male	24	44,4
Operation	TNTS	47	87,0
	Repeat TNTS	5	9,2
	Sublabial	2	3,7
Apoplexy	No	49	94,5
	Yes	3	5,5
Opening	Standart	51	94,4
	Nasal Flap	3	5,6
Microscope/ Endoscope	Microscope	41	75,9
	Microscope + Endoscope	12	22,2
	Endoscope	1	1,8
Pathology	Pituitary adenoma	33	61,1
	Atypical Pituitary adenoma	7	12,9
	Ratke Cleft Cyst	4	7,4
	Craniopharyngioma	3	5,5
	Meningioma	2	3,7
	Chordoma	1	1,8
	Pituitary Hyperplasia	1	1,8
	Adenocarsinoma	1	1,8
	Chondorosarcoma	1	1,8
	Diffuse B- cell Lenfoma	1	1,8
Complications During Surgery	No CSF	22	40,7
	Yes CSF- open suprasellar	16	29,6
	Yes CSF- small	10	18,5
	No CSF- thin arachnoid	4	7,4
TNTS: Transnasal transsphenoidal, CSF: Cerebrospinal Fluid			

Tablo 2. Comparison of the data according to the CSF leak seen or not seen

		CSF leak				
		No		**Yes**		
		n	%	n	%	p
Opening	Nasal Flap	2	3,9	1	33,3	<0,001
	Standart	49	96,0	2	66,6	
Microscope/ Endoscope	Endoscope	1	1,9	0	0	<0,001
	Microscope	39	76,4	1	50,0	
	Microscope + Endoscope	11	21,5	1	50,0	
Complications During Surgery	No CSF	7	13,7	1	50,0	0,009
	Yes CSF	15	29,4	1	50,0	
Closure	Fat and Facia + Surgicel	13	25,4	0	0	<0,001
	Fat and Facia + Surgicel + Fibrin glue	2	3,9	0	0	
	Fat and Facia + Surgicel + Fibrin glue + Septal Flap	1	1,9	0	0	
	Fat and Facia + Surgicel + Septal Flap	1	1,9	0	0	
	Fat and Fascia	1	1,9	0	0	
	Fat Graft	16	31,3	1	50,0	
	Fat Graft + Fibrin Glue	1	1,9	0	0	
	Septal Flap + Fibrin Glue	1	1,9	1	50,0	
	Nothing	15	29,4	0	0	
Lumber puncture	No	40	78,4	1	50,0	1,000
	Yes	11	21,5	1	50,0	
Lumber drenaige	No	42	82,3	1	50,0	<0,001
	Yes	9	17,6	1	50,0	
CSF: Cerebrospinal Fluid						

DISCUSSION

Transsphenoidal (TNTS) surgery has become a standard procedure for different kind of sellar and parasellar lesions in the last two decades. Since Schloffer, who described the TNTS with the transnasal approach in 1907, TNTS has experienced improvements over time and every neurosurgeon has introduced their own special interventions (*5).* Halstead and Cushingused the sublabial approach until the current pituitary approach was converted to the transcranial surgery by the Dandy and Krause (6). Although the TNTS is known as a simple and practical procedure, because of the mortal complications such as CSF leaks, meningitis, hypothalamic and vascular injuries, it had been abandoned at that time. Afterward, this procedure was popularized by Hardy with the involvement of the microscope in surgery (7). Also, transsphenoidal surgery has become more performable with the use of further technological advancements like endoscope by Jho and Carrau in 1997 (8).

TNTS is an effective and safe procedure for most of the sellar and parasellar lesions that can be reached from the sphenoid sinus. This procedure is not only used for pituitary adenomas but also for other kinds of skull base tumors such as craniopharyngiomas, Rathke cleft cysts, meningiomas, chordomas, chondrosarcomas, and metastases. The mortality rates are reported between 0 and 1.4% recently. Although the complications are extremely rare and treatable, are still possible. These include diabetes insipidus, anterior pituitary gland injury, intracranial hematoma, nasal septum perforation, carotid artery injury, sinusitis, central nervous system injury, CSF fistula, and meningitis (9).

In contemporary medical practice, the endoscopic endonasal transsphenoidal approach allows the visualization of more possible cavities inside a confined space. This technique overcomes traditional microscopic procedures' limitations by accessing previously inaccessible structures. Consequently, patients benefit from improved eyesight, improved tumor resection outcomes, and reduced hospitalization durations (10). Furthermore, difficulties related to CSFfistulas can persist, leading to prolonged hospitalization, heightened reliance on antibiotics for the treatment of meningitis, and increased morbidity.Our study aimed to investigate the etiology of CSF fistula in the context of surgical approaches to the sellar area. We also aimed to evaluate the outcomes associated with different closure and post-operative procedures.

Furthermore, CSF leakage was identified in a 76.4% patients using a microscope alone. Similarly, when a microscope and an endoscope were utilized in tandem, CSF leakage was observed in only 5 out of 72 patients. This finding suggests that using a microscope may be more effective in identifying and treating a CSF fistula. The meta-analysis findings indicate a greater incidence of CSF leakage following endoscopic surgery (11) . This finding aligns with the outcomes observed in our surgical procedures.

CSF fistula is a common intraoperative complication, particularly in cases involving malignancies requiring access to the suprasellar region. In order to access the suprasellar space, it is necessary to go through the arachnoid membrane, which creates contact with the CSF. The outcome is expected. Preserving the integrity of the arachnoid membrane during surgical procedures is paramount, unless deemed essential. In situations of this type, autologous materials have been suggested as potential solutions, including mucosal grafts sourced from the middle turbinate, fat grafts obtained from the abdomen region, muscle grafts derived from the lateral thigh, and fascia grafts harvested from the fascia lata, lateral thigh, or temporal muscle (12).

When unexpected access or opening of the suprasellar area occurs, a combination of fat and fascia grafts is employed. To secure the grafts, surgicel is utilized, followed by the application of fibrin glue (13). In instances when noCSF leakage was detected, our approach often involved either choosing not the graft usage or only employing a fat graft. In addition, our preference was mostly towards utilizing fat grafting in cases where a thin arachnoid membrane was observed, evenwithout visualization of CSF. In situations when a minor CSF fistula was observed, the usual approach involves the insertion of surgicel with the fat and fascia graft as a means of repair (14).

Additionally, our findings indicate that the utilization of continuous lumbar drainage is a more efficacious approach for managing CSFcompared to intermittent lumbar puncture. The reason for this phenomenon is that continuous drainage has a greater efficacy in reducing CSF pressure and facilitating the healing process of the membrane. Despite the performance of lumbar puncture, unregulated fluctuations in CSFpressure continue to result in the occurrence of CSF leakage.

CONCLUSION

Cerebrospinal fluid (CSF) leakage is a commonly seen complication in both endoscopic and microscopic transsphenoidal surgeries. It has been suggested that selecting an appropriate closure approach should be based on the intraoperative complications observed during the surgical procedure, to prevent CSF leakage.

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Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

Study Concept / Design : HSC, EU

Data collecting : EU

Data Analysis / Interpretation : HSC

Text Draft : HSC

Technical Support / Material Support : EU

Critical Review of Content : EU

Literature Review : HSC

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Genişlemiş Spektrumlu Beta Laktamaz Üreten *Escherichia coli*'nin Neden Olduğu Üriner Sistem İnfeksiyonlarında Aynı Etkenin Dışkıda Taşıyıcılığının Saptanması

Investigation of carriage of the same strain in feces in Urinary System Infections Caused by Extended Spectrum Beta-Lactamase Producing *Escherichia coli* Strains

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Özet

Giriş-Amaç: GSBL (+) *E. coli*'nin neden olduğu ÜSİ'de aynı etkenin dışkı kolonizasyonunun ve hem idrar hem de dışkı izolatlarından elde edilen fenotipik olarak benzer etkenlerin moleküler olarak birbirleriyle benzerliklerinin araştırılması ve GSBL (+) *E. coli* kaynaklı ÜSİ' lerde risk faktörleri, fekal taşıyıcılığın infeksiyona katkısı ve infeksiyonun önlenmesinde alınması gereken önlemlerin belirlenmesi amaçlanmıştır.
Yöntem: Tek merkezli, ileriye dönük, kesitsel çalışmada idrar kültüründe GSBL üreten *E.coli* izole edilen, 18-79 yaş aralığında 64 hasta çalışmaya dahil edildi. Hastalardan alınan dışkı örnekleri sefotaksim ve seftazidim içeren içeren EMB agara ekildi ve *Enterobacteriaceae* ailesine ait kolonilerin identifikasyonunda IMVIC testi kullanıldı. Üreme özelliklerine göre *E. coli* olarak belirlenen suşlar çalışmaya alındı. GSBL taşıyan kökenlerin tespiti için fenotipik doğrulama testleri ve DNA izolasyonu için ERIC PCR yöntemi kullanıldı.Tanımlayıcı istatistikler sayı ve yüzde olarak ifade edildi. Analitik karşılaştırmalar için ki-kare ve trend ki –kare testleri kullanıldı. $p<0.05$ değeri istatistiksel olarak anlamlı kabul edildi.
Bulgular: 64 hastanın 40'ı (%62.5) kadın ve yaş ortalaması 56.5 ± 17.5 (18-79) idi. Hastaların 47 (%69)' si TK 17 (%31)' si ise HK-ÜSİ tanısı almıştı.Yılda üçten fazla ÜSİ atağı geçirmek ve yabancı cisim bulunması TK-GSBL (+) *E. coli'* ye bağlı ÜSİ için risk faktörü olarak bulunmuştur (*p*:0.035 ve 0.006). 64 hastanın 15 (%23)'inde ÜSİ tedavisi sonrası GSBL (+) *E. coli*'nin fekal kolonizasyonunun persiste ettiği ve bunların üç (%20)' ünün dışkı ve idrar izolatlarının aynı filogenetik sınıfta olduğu bulunmuştur. Son bir yılda invazif girişim varlığı olanlarda fekal kolonizasyon anlamlı olarak yüksek saptanmıştır (*p*:0.037).
Sonuç: Dirençli infeksiyonlar ve kolonizasyon artışı nedeni ile gereksiz antibiyotik kullanımı önlenmelidir. GSBL üreten bakterilerle meydana gelen infeksiyonlarda fekal kolonizasyonun önemi ve GSBL enzim tiplerinin epidemiyolojisinin anlaşılabilmesi için ileriye dönük daha büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Üriner Sistem İnfeksiyonu, Fekal Kolonizasyon, GSBL üreten *E. coli.*

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Abstract

Introduction-Objective: We aimed to determinate the risk factors, contribution of fecal carriage to the infection and precautions to be taken in the prevention of infection in (+) *E. coli*-induced UTIs in urinary tract infections (UTI) caused by ESBL (+) *E. coli*

Method: This study was designed as a single-center, prospective and cross-sectional. 64 patients between the ages of 18-79 who were hospitalized and ESBL(+) *E.coli* isolated in their urine culture were included. Stool samples taken from the patients (0,3,5 and 7 days) were inoculated on EMB agar containing cefotaxime and ceftazidime and IMVIC was used to identify colonies. Strains determined as *E. coli* according to their reproductive characteristics were included in the study. Phenotypic confirmation tests for the detection of ESBL(+) strains. Genotyping was performed using the ERIC PCR method. Descriptive statistics were expressed as numbers and percentages. Chi-square and trend chi-square tests were used for analytical comparisons. A P value of <0.05 was considered statistically significant.

Results: Of the 64 patients 40 (62.5%) were female and the mean age was 56.5 ± 17.5 (18-79). 47 (69%) were diagnosed with CA- UTI, and 17 (31%) with HA-UTI. Having more than three episodes per year and presence of a foreign device were found to be a risk factor for CA- ESBL (+) *E. coli*-induced UTI (p:0.035and 0.006). It was found that faecal colonization of ESBL (+) *E. coli* persisted in 15 (23%) of 64 patients after UTI treatment, and, of them 20% (n: 3) was in the same phylogenetic class with the ERIC PCR method. Faecal colonization was found to be significantly higher in patients with invasive intervention in the previous year (p:0.037).

Conclusion: Unnecessary antibiotic use should be avoided due to resistant infections and increased colonization. The importance of fecal colonization in infections with ESBL-producing bacteria (especially UTI) has been demonstrated in studies. More prospective studies are needed to understand the epidemiology of ESBL enzyme types.

Keywords: Urinary Tract İnfection, Faecal Colonisation, ESBL Producing *E. coli*.

GİRİŞ

Escherichiacoli (*E. coli*), sağlıklı insan ve hayvanların barsak florasında bulunan Enterobacterales ailesinin bir üyesidir. Hastane kökenliden (HK) daha ziyade toplumdan edinilmiş batın içi infeksiyon, üriner sistem infeksiyonu (ÜSİ) ve pelvik inflamatuvar hastalık gibi durumlarda sıklıkla görülür. Toplum kökenli (TK) ÜSİ'lerin %85'inden fazlasında etken E. coli olarak saptanmıştır (1). Diğer taraftan özellikle geniş spektrumlu sefalosporinlerin yaygın kullanımı sonucunda gelişen antimikrobiyal direnç tedavi seçeneklerini kısıtlamaktadır (2,3). Genişletilmiş spektrumlu beta-laktamaz (GSBL) gibi enzimler penisilinler, sefalosporinler ve monobaktamlar dahil olmak üzere en sık kullanılan antibiyotiklerin bazılarına karşı direnç kazandırabilen ve onları parçalayabilen bakteriler tarafından üretilen enzimler olup E. coli dahil olmak üzere patojenik bakterilerde giderek artmaktadır. GSBL üreten mikroorganizmalar tüm dünyada HK infeksiyonların en önemli nedenidir (4). Ancak son yıllarda toplum kökenli infeksiyonlarda da sıkça saptanmaktadır. TK ÜSİ'de GSBL üreten *E. coli* oranı Çin'de % 45.2-68.2, ABD'de %6.5'den %16'ya arttığı bildirilirken Kuzey Avrupa ülkelerinde prevalans %5'in altındadır (5-8). Ülkemizde GSBL üreten *E.coli* prevalansının TK ÜSİ'de %38.2'lerde olduğu bildirilmiştir (9). GSBL üreten bakterilerle oluşan hastane ya da toplum kökenli infeksiyonların epidemiyolojisi ve klinik öneminde gastrointestinal sistem kolonizasyonu anahtar rol oynar. Bu bakterilerin neden olduğu infeksiyonların çoğunda barsak kolonizasyonu gösterilmiştir (10). Toplumdan gelen hastalarda GSBL üreten Enterobacterales'e bağlı gelişen infeksiyonlar ve fekal kolonizasyon arasındaki ilişki araştırılmış ve fekal kolonizasyonu olan hastaların %15.4'ünde bakteremi geliştiği gösterilmiştir (11). 2003-2007 yılları arasında Avrupa'da sağlıklı kişilerde fekal kolonizasyon oranı %1-8 arasında bildirilirken (10,12) yakın zamanda yapılan bir derleme ve meta-analizde prevalansın %21.1'e ulaştığı görülmüştür (13). Ülkemizde GSBL üreten

bakterilerin fekal kolonizasyonunu araştıran çalışmalarda bu oran %15.2-30 arasında değişmektedir (14-17).

Bu çalışma ile GSBL üreten *E.coli*'nin neden olduğu ÜSİ tanısı alan hastalarda aynı etkenin fekal kolonizasyonunun araştırılması, hem idrar hem de dışkı izolatlarından elde edilen fenotipik olarak benzer etkenlerin moleküler olarak filogenetik sınıflamasının yapılması ve birbirleriyle benzerliklerinin araştırılması, bu suşların etken olduğu ÜSİ'deki risk faktörlerinin ve fekal taşıyıcılığın infeksiyona katkısının belirlenmesi amaçlanmıştır.

YÖNTEM

Hasta Seçimi

Çalışma tek merkezli, ileriye dönük ve kesitsel olarak dizayn edildi. Mayıs 2011-Haziran 2014 tarihleri arasında Kocaeli Üniversitesi Hastanesi'ne ayaktan ÜSİ tanısı alarak yatırılan ya da hastanede yatışı sırasında CDC (18) kriterlerine göre HK ÜSİ tanısı alan, idrar kültüründe GSBL üreten *E.coli* izole edilen, 18-79 yaş aralığında 64 hasta çalışmaya dahil edildi. 18 yaş altı- 79 yaş üzerinde, yoğun bakım ünitesinde (YBÜ) yatan ve onam formunu doldurmayan hastalar dahil edilmedi. Çalışma Kocaeli Üniversitesi Bilimsel ve Klinik Araştırmalar Etik Kurul'u tarafından 27.12.2010 tarih ve 2010/19 proje numarası ile onaylandı.

Epidemiyolojik ve Klinik Veriler

ÜSİ tanısı alan, idrar kültüründe GSBL sentezleyen *E.coli* üreyen hastaların yaşı, cinsiyeti,altta yatan hastalığı, semptomları, son üç ayda hastane yatışı, en az 48 saat süreyle antibiyotik kullanımı ve bir haftadan uzun idrar veya diğer kateter (üreteral stent, nefrostomi, sistostomi kateteri) bulunması, üriner anomali (fonksiyonel, anatomik ya da renal), tekrarlayan ÜSİ (son bir yılda üçten fazla yada son altı ayda en az bir atak), son bir yılda cerrahi operasyon ya da girişim (ürolojik, gastroenterolojik, jinekolojik ya da diğer girişimler) öyküsü hasta formlarına kaydedildi.

Örneklerin Toplanması ve Bakteri Tanımlanması

Hastalardan alınan dışkı örneklerinin 0,5 g'ı 5 ml salin çözeltisiyle süspanse edildi ve her bir agara200 mL örnek konulacak şekilde 1µg/mL sefotaksim (CTX) içeren Eosin Methylene-blue Lactose Sucrose (EMB) (Salubris, Türkiye) agara, 1µg/mL seftazidim (CAZ) içeren EMB agara ve üreme kontrolü amacı ile antibiyotiksiz EMB agara ekildi. Bakterileri identifiye etmek üzere üç şeker, triptofandan indol oluşturma, Metil kırmızısı, Voges-Proskauer ve sitrat testi (IMVIC) yapıldı. Üreme özelliklerine göre *E. coli* olarak belirlenen izolatlar çalışmaya alındı. GSBL taşıyan kökenlerin tespiti için CLSI önerilerine göre (19) önerilen şekilde fenotipik doğrulama testlerinden çift disk sinerji testi ve kombinasyon disk yöntemi uygulandı. Seftazidim diskine kıyasla seftazidim/klavulanat diskizon çapındaki ≥5 mm'lik artış GSBL enzimi taşıyan izolat olarak çalışmaya alındı. *E.coli* ATCC 25922 suşu kontrol suş olarak kullanıldı.

Deoksiribonükleik Asit (DNA) İzolasyonu

Tek koloni düşürme yöntemiyle elde edilen bir koloni, aseptik şartlar altında mikrosantrifüj tüpü içerisindeki 1 ml Luria-Bertani Buyyon (LB) besiyerine ekilerek 37 ± 2 ºC'de inkübe edildi. Elde edilen bakteri DNA'larına Enterobacterial Repetitive Intergenic Consensus Sequences (ERIC) PCR yöntemi kullanılarak genotipleme yapıldı. ERIC-1 (ATGTAAGCTCCTGGGGATTCAC) ve ERIC-2 (AAGTAAGTGACTGGGGTGAGCG)

primerleri daha önceki bir çalışmadan alındı. (20). Her bir primer dizisinden (Qiagen, Almanya), firma önerisine göre stok çözelti elde edildi. Tepkime iCycler (BioRad, USA) termal cyclerda gerçekleştirildi. Oluşan ürünlerin gözlemlenmesi için yatay jel elektroforezi kullanıldı. Sonuçlar, GeneLine Image SCI (Spectronics Corp., USA) jel görüntüleme sisteminde değerlendirildi.

İstatistiksel Analiz

Verilerin değerlendirilmesinde 'SPSS Statistics 21.0 for Windows Student Version' istatistik programı kullanıldı. Tanımlayıcı istatistikler sayı ve yüzde olarak ifade edildi. Analitik karşılaştırmalar için ki-kare ve trend ki –kare testleri kullanıldı. $P<0.05$ değeri istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışma süresince 18-79 yaş aralığında, idrar kültüründe GSBL üreten *E.coli* izole edilen ve TK ÜSİ tanısıyla 47 ve HK ÜSİ tanısıyla 17 hasta olmak üzere toplam 64 hasta çalışmaya dahil edilmiştir. Hastaların 40'ı (%62.5) kadın ve yaş ortalaması 56.5 ± 17.5 idi. 32 (%50) komplike ÜSİ, 30 (%46.8) piyelonefrit ve iki hasta (%3.2) ise prostatit tanısı aldı. Hastaların demografik ve klinik özellikleri Tablo 1'de gösterilmiştir.

Tablo 1. Hastaların Demografik ve Klinik Özellikleri

	n (%)
Yaş, mean (SD)	56.5 ± 17.5
Cinsiyet (kadın)	40 (62.5)
Komorbidite	
HT	32 (50)
KBH	25 (39)
DM	23 (36)
Malignite	22 (34.3)
Nörojen mesane	4 (6.2)
Otoimmün hastalık	4 (6.2)
Renal transplantasyon	2 (3.1)
Yatış tanısı	
Komplike ÜSİ	32 (50)
Piyelonefrit	30 (46.8)
Prostatit	2 (3.2)
Semptomlar	
Dizüri.	49 (76.5)
Pollaküri	36 (56.2)
Ateş	34 (53.1)
Suprapubik hassasiyet	24 (37.5)
Yanağrısı	21 (32.8)
Bulantı ve kusma	2 (3.1)
İnfeksiyon türü	
TK ÜSİ	47 (73.5)
HK ÜSİ	17 (26.5)

HT: Hipertansiyon, KBH: Kronik Böbrek Hastalığı, DM: Diabetes Mellitus, ÜSİ: Üriner Sistem İnfeksiyonu, TK: Toplum Kökenli, HK: Hastane Kökenli.

GSBL üreten E.coli'ye bağlı TK ve HK ÜSİ'lerde tüm izolatların ampisilin, sefazolin, sefepim, seftazidim ve seftriaksona dirençli ve ertapenem, meropenem ve tigesikline duyarlı

olduğu saptanmıştır. İzolatların direnç durumları karşılaştırıldığında istatistiksel anlamlı farklılık bulunmadı (p>0.05). (Tablo 2).

Tablo 2. Toplum ve Hastane Kökenli *E. coli* İzolatlarında Direnç Oranları (n: hasta)

Antibiyotik	Toplum (%) n: 47	Hastane (%) n:17	p
Amikasin	12 (25.5)	5 (29.4)	0.758
Amoksisilin/klavulanat	35 (74.5)	13 (76.5)	0.871
Seftazidim	47 (100)	17 (100)	-
Sefepim	47 (100)	17 (100)	-
Sefoksitin	15 (31.9)	8 (47.1)	0.269
Seftriakson	47 (100)	17 (100)	-
Fosfamisin	24 (51.1)	8 (47.1)	0.779
Nitrofurantoin	29 (61.7)	8 (47.1)	0.299
Ertapenem	-	-	-
Meropenem	-	-	-
Gentamisin	21 (44.7)	9 (52.9)	0.562
Siprofloksasin	39 (83)	16 (94)	0.261
Piperasilin/tazobaktam	13 (27.7)	7 (41.2)	0.307
Trimetoprim/sulfametaksazol	36 (76.6)	14 (82.4)	0.625

Hastalar TK ve HK ÜSİ risk faktörleri açısından karşılaştırıldığında tekrarlayan ÜSİ geçirmek ve yabancı cisim bulunması toplum kökenli ÜSİ'de anlamlı olarak yüksek bulunmuştur (p:0.035 ve p: 0.006). Son üç ayda antibiyotik kullanımı, üriner disfonksiyon ve son bir yılda gastroenterolojik, ürolojik ya da jinekolojik girişim öyküsü açısından karşılaştırıldığında anlamlı farklılık bulunmadı (Tablo 3).

Tablo 3. Toplum ve Hastane Kökenli ÜSİ'de Risk Faktörleri (n: hastalar)

	Toplum Kökenli n: 47	Hastane Kökenli n: 17	p
Tekrarlayan ÜSİ, n (%)			
Yılda 3 ya da ↑	33(76)	10(24)	
6 ayda 1 ya da ↑	12(92)	1(8)	**0.035**
Son 3 ayda 48 h ↑ antibiyotik, n (%)	41(87)	6(94)	0.439
Yabancı cisim, n (%)			
Foley	6(12.8)	6(35.3)	
TAK	3(6.4)	2(11.8)	**0.006**
Nefrostomi	3(6.4)	3(17.6)	
Üreteralstent	5(10.6)	1(5.9)	
Sistostomi	-	1(5.9)	
Üriner disfonksiyon, n (%)	38 (81)	14 (82)	0.893
Son 1 yılda girişim, n(%)	33(46)	11(64)	0.564

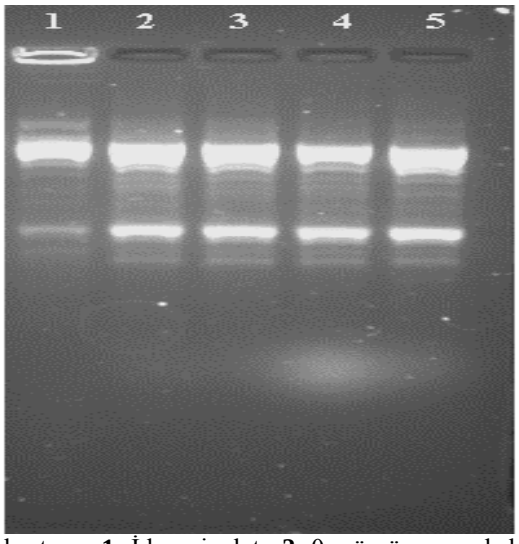
ÜSİ: Üriner Sistem İnfeksiyonu, TAK: Temiz Aralıklı Kateter.

Hastaların GSBL üreten E.coli ile fekal kolonizasyonuna bakıldığında, alınan dört dışkı ya da rektal sürüntü kültürlerinin tümünde (sıfır, üç, beş ve yedinci günlerde alınan kültürler) GSBL üreten *E.coli* saptanması fekal kolonizasyon olarak değerlendirildi. 15 (%23) hastada fekal kolonizasyon saptandı. Fekal kolonizasyon riskini 60 yaş üzerinde olmak ve ürogenital girişim öyküsü anlamlı olarak arttırdığı bulundu (p: 0.036 ve p: 0.037) (Tablo 4).

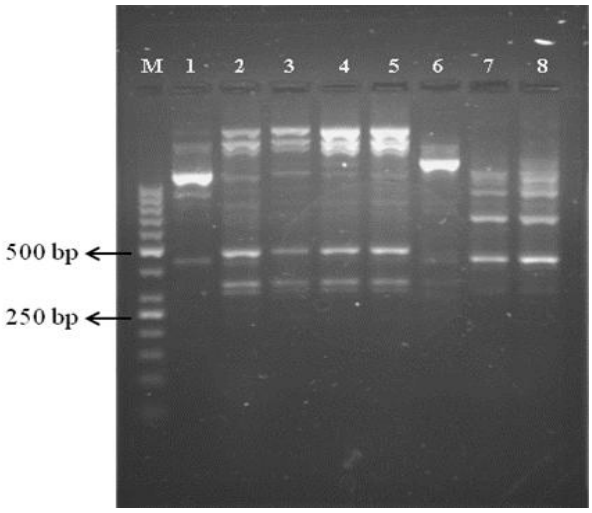
Tablo 4. Fekal Kolonizasyon Risk Faktörleri

Fekal Kolonizasyon	n(%)	p
Girişim, n(%) Ürogenita Gastroenterolojik	 l12(43) 1(20)	**0.037**
Yaş, n(%) 18-39 40-59 60 ve ↑	 1(7) 2(13) 12(80)	**0.036**

GSBL üreten *E. coli* ile fekalkolonize15 hastanın idrardan izole edilen suşlarının filogenetik sınıflamasına bakıldığında, üç (%20) hastada benzerlik saptandı. Bu hastaların ikisi (%66.6) TK ÜSİ tanısı almıştı. Altta yatan hastalıkları KBH (%66.6) ve maligniteydi (%33.3). Hastaların filogenetik gruplarına ait jel elektroforez görüntüleri Şekil 1a ve 1b'de gösterilmiştir.



Şekil 1a. Fekal kolonize2 no'lu hastanın **1**: İdrar izolatı, **2**: 0. gün üreyen dışkı izolatı, **3**: 3. gün üreyen dışkı izolatı, **4**: 5. gün üreyen dışkı izolatı, **5**: 7. gün üreyen dışkı izolatına ait jel görüntüsü. İdrar ve dışkı izolatlarının aynı filogenetik gruba ait olduğu gösterilmiştir.



Şekil 1b. İdrar ve dışkı suşları arasında filogenetik benzerlik bulunmayan fekal kolonize iki hastaya ait jel görüntüleri. M: Marker, **1**: Hasta no. 15 idrar izolatı, **2**: Aynı hastanın 0. gün dışkı izolatı, **3**: Aynı hastanın 3. gün dışkı izolatı, **4**: Aynı hastanın 5. gün dışkı izolatı, **5**: Aynı hastanın 7. gün dışkı izolatı**, 6**: Hasta no.27 idrar izolatı, **7**: Aynı hastanın 0. gün dışkı izolatı, **8:** Aynı hastanın 3. gün dışkı izolatı.

TARTIŞMA

Bu çalışmada 64 hastanın 15 (% 23)'inde fekal kolonizasyon saptandı. 60 yaş üzerinde olmak ve son bir yılda ürogenital girişim yapılmasının kolonizasyonu anlamlı olarak arttırdığı bulunmuştur (Tablo 4). İspanya'da yapılan vaka-kontrol çalışmasında CTX-M ve SHV-TEM üreten izolatlar için üriner kateterizasyonun GSBL (+) *E. coli* ile nozokomiyal infeksiyon/kolonizasyon açısından risk faktörü olduğu gösterilmiştir. Geçmişte beta laktam grubu antibiyotik kullanımı ve DM, CTX-M üreten izolatlar için bağımsız risk faktörü olarak bulunurken, florokinolon kullanımı SHV-TEM için risk faktörü olarak bulunmuştur (21). Colodner ve ark.'nın yaptığı çalışmada GSBL (+) TK ÜSİ için bağımsız risk faktörleri olarak; son üç ayda hastane yatışı ve antibiyotik kullanımı, 60 yaş üzerinde olmak, DM ve erkek cinsiyet bulunmuştur (22). Çalışmamızda da GSBL (+) TK ÜSİ için yılda 3'ten fazla ÜSİ atağı geçirmek ve üriner kateter varlığı risk faktörleri olarak bulunmuş olup diğer çalışmalarla benzerdir.

TK GSBL'yi araştıran başka bir çalışmada ise bakımevinde yaşamak ve kronik obstrüktif akciğer hastalığı (KOAH) infeksiyon için bağımsız risk faktörü olarak saptanmış (23). Bizim çalışmamızda vakalarımızın hiç birisinde KOAH yoktu ve en sık komorbiditeler ise HT, KBH ve DM idi. (%50, %39 ve %36).

Çalışmalarda son üç ayda 2. ve 3. kuşak sefalosporin ile kinolon kullanımının GSBL üretimini arttırdığı gösterilmiştir (22,24). Diğer taraftan ülkemizden Azap ve ark.'nın yaptığı çalışmada ise son üç ayda beta-laktam antibiyotik kullanımının GSBL üretiminde bağımsız risk faktörü olduğu gösterilmiştir (15). Bizim çalışmamızda ise, GSBL'nin neden olduğu TK ÜSİ'lde son üç ayda antibiyotik kullanım oranı %87, HK ÜSİ'de ise %94 olarak bulundu ve en sık kullanılan antibiyotik kinolonlardı. Fakat gruplar arasında istatistiksel anlamlı farklılık görülmedi.

GSBL üreten suşlarla meydana gelen infeksiyonların yıllar içinde hastane ve toplumda görülme oranlarındaki dikkati çeken artış olmaktadır. Bu oranın kıtalar bazında %2 ile %46 arasında olduğu ve sağlıklı kişiler arasındaki taşıyıclıkta ise her yıl %5'lik bir artış olduğu tahmin edilmektedir (25). Ülkemizde yapılan çalışmalarda *E. coli* ve *Klebsiella pneumoniae* (*K. pneumoniae*) infeksiyonların yarısının HK ÜSİ'den ve GSBL üreten *E. coli* türlerinin ise %24'ünün TK ÜSİ'den sorumu olduğu gösterilmiştir (9,26).

Yakın zamanda yapılan bir çalışmada hastanede yatan hastalarda son altı ayda geniş spekrumlu antibiyotik kullanımı, total parenteral beslenme ve uzamış hastane yatışının GSBL üreten *K.pneumoniae* ve *E. coli*'nin fekal kolonizasyonunu anlamlı olarak arttırdığı gösterilmiştir (27). Antibiyotik kullanımı barsak florasınının inhibisyonuna neden olarak antibiyotik dirençli Gram-negatif bakterilerin proliferasyonuna ve bu bakterilerin florada seçilmesine katkıda bulunmaktadır. Antibiyotik kullanımı ile gastrointestinal sistemde GSBL üreten mikroorganizmalar seçilmekte bu da GSBL üreten bakterilerle meydana gelen infeksiyonların oluşumu için ön koşul olan kolonizasyona neden olmaktadır (28).

Bununla birlikte sosyoekonomik faktörler, beslenme alışkanlıkları, barınma koşulları ve yüksek endemisite gösteren ülkelere seyahatin toplumda GSBL üreten veya karbapenem dirençli kökenlerin fekal kolonizasyonu için potansiyel risk faktörleri olabileceği vekolonize olan asemptomatik kişilerin GSBL üreten bakterilerin toplumda yayılmasına katkıda sağlayacağı bildirilmiştir (29). GSBL üreten *E.coli*'nin neden olduğu ÜSİ'de fekal taşıyıcığı araştıran az sayıda çalışma olmasına karşın, çok merkezli yapılan bir çalışmada idrar ve dışkı örneklerinde saptanan *E.coli'*nin filogenetik benzerliği %22.6 olarak bulunmuştur. Bizim çalışmamızda da persistan fekal taşıyıcılık oranı %23 ve bunların %20'sinin idrar izolatıyla

filogenetik olarak benzeştiği bulunmuştur. GSBL üreten *E.coli*'nin neden olduğu ÜSİ'de, öncesinde antibiyotik almayan ve idrar ile dışkı izolatı benzerlik gösteren kişilerde fekal taşıyıcılığın ÜSİ gelişimiyle ilişkili olduğu gösterilmiştir (30).

Sağlık bakımı hizmeti veren merkezlerde dirençli suşların yayılmasının önlenmesinde temas izolasyon önlemlerinin uygulanması ve hastaların izole birimlerde takip ve tedavisinin sürdürülmesi önerilmekte fakat düşük direnç profiline sahip ülkelerde bile beraberinde getireceği uygulama zorluğu ve mali yükün de göz önünde bulundurulması gerekliliği vurgulanmaktadır (31,32). Çoklu ilaca dirençli mikroorganizmaların artmaya devam etmesi ve küresel bir tehdit oluşturması nedeniyle, kolonize hastalardan kaynaklı yayılımın önlenmesinde hastaların belirli özellikleri ve gereksinimlerinin değerlendirilerek merkezler bazında etkili önlemleri dikkate alması en akılcı yaklaşım olacaktır.

SONUÇ

Sonuç olarak, çalışmamızda son bir yılda üç ve daha fazla infeksiyon atağı geçirmek ve üriner sistemde yabancı cisim bulunması TK ÜSİ için ve ürogenital girişim öyküsü ile 60 yaş üzeri olmak ise persistan fekal kolonizasyon açısından anlamlı risk faktörleri olarak saptanmıştır.TK ve HK infeksiyonlar açısından önemi gittikçe artan GSBL üreten bakterilerin neden olduğu fekalkolonizasyonun risk faktörlerinin belirlenmesi ve ÜSİ'deki rolünün anlaşılması için daha kapsamlı ve geniş serileri içeren prospektif çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Çıkar Çatışması Beyanı: Çıkar çatışması bulunmamaktadır.

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Not: Bu çalışma 01.04.2015 5. EKMUD Bilimsel Platformunda PS:088 numaralı poster sunum olarak sunulmuştur.

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Diabetik Ayak Enfeksiyonları

Diabetic Foot Infections

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Özet

Giriş: Son yıllarda tüm dünyada ve Türkiye'de görülme sıklığının hızla arttığını göz önüne alırsak Diabetes mellitus (DM); önemli bir uluslararası halk sağlığı sorunu haline gelmiştir. Diyabetik ayak DM'nin ciddi ve sık görülen kronik komplikasyonlarından biridir.
Amaç: Bu çalışmada diyabetik hastaları değerlendirerek ; hastalarda diyabetik ayak ülserleri ile ilişkili prognoz ve diğer etkili faktörleri ortaya koymayı amaçladık.
Yöntem: Çalışmamız 2012 ile 2020 yılları arasında,diyabetik ayak enfeksiyonu tanılı 64 hasta dahil edilmiştir. Hastaların demografik, klinik ve laboratuvar bulguları, bilateral alt extremite arteriyel ve venöz Doppler ultrasonografi bulguları, altta yatan hastalıkları, yara genişliği, tedavide kullanılan antibiyotikleri retrospektif olarak elde edilmiştir.
Bulgular: Çalışmaya 21 kadın (%33) ve 43 erkek (%67) olmak üzere toplam 64 kişi dahil edilmiştir. Bu hastaların 33'ü (%52) oral anti diyabetik kullanırken 19'u (%30) insülin kullanmakta idi. Hastaların %53'ünde periferik arter hastalığı ve (%62,5) koroner arter hastalığı tanısı vardı. 3'ü (%4,7) kronik böbrek hastalığı olup 2'si (%3) hemodiyaliz tedavisi almaktaydı. Hastaların 30'unda (%47) hipertansiyon mevcuttu. Yara genişliği ≥5cm olan 27 (%42) hasta mevcuttu. Hastalarda sağ ayak etkilenmesi (n=40, %62,5) daha fazlaydı. 10 (%16) hastanın derin doku kültüründe üreyen mikroorganizmalar ise 3 hastada K*lebsiella pneumoniae*, 1 hastada *Klebsiella oxytoca*, 2 hastada Metisiline dirençli *Staphylococcus aureus*, 2 hastada *Morganella morganii*, 2 S*erratia marcescens* tespit edildi.
Sonuç: Diyabetik ayak ülserlerinin uygun şekilde değerlendirilmesi ile infeksiyona bağlı morbidite, hastaneye yatış, hastanede kalış süresi ve majorekstremite ampütasyonu oranları azaltılabilmektedir.

Anahtar Kelimeler: Diabetes Mellitus, Diyabetik Ayak Enfeksiyonları, Doppler USG, Periferal Arter Hastalığı.

Abstract

Introduction: Diabetes mellitus (DM) has become an important international public health problem considering that its prevalence has increased rapidly in Turkey and all over the world in recent years. A serious and common chronic complication of DM is diabetic foot.
Objective: We aimed to evaluate diabetic patients and to determine the prognosis and other effective factors associated with diabetic foot ulcers in patients.

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Method: In this study, 64 patients diagnosed with diabetic foot infection between 2012 and 2020 were included. Demographic, clinical and laboratory findings, bilateral lower extremity arterial and venous Doppler ultrasonography findings, underlying diseases, wound width, antibiotics used in treatment were obtained retrospectively.
Results: A total of 64 patients, 21 females (33%) and 43 males (67%), were included in the study. Of these patients, 33 (52%) were using oral anti-diabetics and 19 (30%) were using insulin. 53% of the patients had a diagnosis of peripheral artery disease and (62.5%) coronary artery disease. 3 (4.7%) had chronic kidney disease and 2 (3%) were receiving haemodialysis treatment. Hypertension was present in 30 (47%) of the patients. 27 (42%) patients had a wound width ≥5cm. Right foot was more commonly affected (n=40, 62.5%). In 10 (16%) patients, the microorganisms grown in deep tissue culture were *Klebsiella pneumoniae* in 3 patients, *Klebsiella oxytoca* in 1 patient, *Methicillin-resistant Staphylococcus aureus* in 2 patients, *Morganella morganii* in 2 patients, *Serratia marcescens* in 2 patients.
Conclusion: With proper evaluation of diabetic foot ulcers, infection-related morbidity, hospitalisation, length of hospital stay and major limb amputation rates can be reduced.

Key words: Diabetes Mellitus, Diabetic Foot Infections, Doppler Ultrasonography, Peripheral Artery Disease.

GİRİŞ

Diabetes mellitus (DM); kan glukoz seviyesinin normalin üzerine seyretmesi ile karakterize sistemik komplikasyonlara seyreden ilerleyici kronik metabolik bir hastalıktır (1). DM'nin dünya çapında mevcut tahmini prevalansı %9,3'tür ve 2030 ve 2045'e kadar sırasıyla %10,2 ve %10,9'a ulaşacağı tahmin edilmektedir (2). Son yıllarda tüm dünyada ve Türkiye'de görülme sıklığının hızla arttığını göz önüne alırsak DM; önemli bir uluslararası halk sağlığı sorunu haline gelmiştir (3,4). Diyabetik ayak DM'nin ciddi ve sık görülen kronik komplikasyonlarından biridir. En önemli iki risk faktörü periferik nöropati (duyusal, motor ve otonom) ve periferik vasküler hastalıklar ; diyabetin kötü kontrolü sonucunda hızlı bir şekilde ortaya çıkabilir (5). Diyabetli hastalarda ayak ülserlerinin gelişiminde rol oynayan birçok faktör vardır. Travma ülser gelişiminde önemli bir rol oynar iken Duyusal nöropati hastanın duyusal farkındalığını azaltır ve travmayı fark edemeyen hasta basınç yaralanmalarına maruz kalır. Zayıf kan akımı (iskemi) yara iyileşmesini engellerken, diyabetik immünosupresyon da eklenince ciddi enfeksiyon olasılığı artar (6). Hastalıklarla ilgili net tanımlar ve kriterler ; bir hastalıkla ilgili iletişim için hayati öneme sahip olmaya devam etmektedir. Bu durum, özellikle multi disipliner bir hastalık olan diyabetle ilişkili ayak hastalığı için de geçerlidir. Farklı bölgelerde yaşayan hastaların ülser tipini tanımlamak için dünya çapında uygulanabilecek bir sistem ile farklı bakım stratejilerinin avantaj ve dezavantajlarının resmi olarak değerlendirilmesi ihtiyaç olmuştur. Diyabetle ilişkili ayak hastalığı tanımları ve kriterler Uluslararası Diyabetik Ayak Çalışma Grubu tarafından 1999 yılından bu yana dikkatle çalışılmış ve bu en son 2023 yılında güncellenmiştir (7).

YÖNTEM

Çalışmamız 2012 ile 2020 yılları arasında hastanemizde yatan 18 yaş üstü ,diyabetik ayak enfeksiyonu tanılı toplam 64 hasta dahil edilmiştir. Hastaların demografik, klinik ve laboratuvar bulguları, bilateral alt extremite arteriyel ve venöz Doppler ultrasonografi (USG) bulguları, altta yatan hastalıkları, yara genişliği, tedavide kullanılan antibiyotikleri, hastanenin elektronik bilgi sisteminden, retrospektif olarak elde edilmiştir. Etik kurul onayları alınmıştır. (12.04.2021 tarihli no:35891)

Bu çalışmada diyabetik ayak için SINBAD sınıflandırması ve PEDİS sınıflandırılması kullanılmıştır: SINBAD Sınıflandırma Sistemi ve Skoru, ciddiyetlerine göre derecelendirilen altı unsurdan gelen bir kısaltmadır: Ülser bölgesi, iskemi, nöropati, bakteriyel enfeksiyon, alan ve derinlik. Toplam skor 0 ile 6 arasında değişmekte olup, alt ekstremite amputasyonu

riskiyle ilgili düşük derece, 0-2; orta derece, 3-4; ve yüksek derece, 5-6 olarak üç kategoriye ayrılmıştır (8).

PEDİS Sınıflaması; perfüzyon (P, perfusion), genişlik/boyut (E, extend/size), derinlik/doku kaybı (D, depth/tissue lost), enfeksiyon (I, infection) ve duyu (S, sensation). Evre 1: İnfeksiyon belirti ve bulgusu yok. Evre 2: ≥2 cm inflamasyon bulgusu (pürülan, eritem, ağrı, hassasiyet, ısı artışı, endurasyon) ülser etrafında selülit/eritem ≤2 cm enfeksiyon cilt veya yüzeyel cilt altı dokuya lokalize. Evre 3: Genişliği 2 cm'nin üzerinde olan eritem ve (şişlik, duyarlılık, sıcaklık, akıntı) en az birisi veya infeksiyonun, apse, osteomyelit, septik artrit veya fasiit biçiminde deri ve deri altı dokularından daha derin yapıları tutması. Evre 4: Sepsis bulgularıyla birlikte herhangi bir ayak infeksiyonu skorlaması yapılmıştır.

İstatistiksel Analiz

Verileri analiz etmek için SPSS versiyon 20.0 istatistik yazılımını kullandık. Niteliksel değişkenler yüzdeler kullanılarak tanımlandı. Normal dağılıma uyan nicel değişkenler ortalama ± SD ile, normal dağılıma uymayan nicel değişkenler Medyan (minimum-maksimum) ile ifade edildi. İstatistiksel anlamlılık, $p < 0.05$ değerinde kabul edildi.

BULGULAR

Çalışmaya 21 kadın (%33) ve 43 erkek (%67) olmak üzere toplam 64 kişi dahil edilmiştir. Hastaların diyabet tiplerine bakıldığında tamamına yakınını (n=62, %97) tip 2 DM oluşturmakta idi. Bu hastaların 33'ü (%52) oral anti diyabetik kullanırken 19'u (%30) insülin kullanmakta idi. Hastaların %53'ünde periferik arter hastalığı (PAH) ve (%62,5) koroner arter hastalığı (KAH) tanısı vardı. 3'ü (%4,7) kronik böbrek hastalığı (KBY) olup 2'si (%3) hemodiyaliz tedavisi almaktaydı. Hastaların 30'unda (%47) hipertansiyon (HT) mevcuttu.Yara genişliği ≥5cm olan 27 (%42) hasta mevcuttu. Hastalarda sağ ayak etkilenmesi (n=40, %62,5) daha fazlaydı (Tablo1).

Tablo 1. Hastaların Demografik Değişkenlerin Dağılımı

Demografik Özellikler		n	%
Cinsiyet	Kadın	21	33
	Erkek	43	67
Yaş	41-55 yaş	13	20,3
	56-65 yaş	16	25,0
	67-76 yaş	16	25,0
	77-90 yaş	19	29,7
Diyabet Tipi	Tip 1	2	3
	Tip 2	62	97
İnsülin kullanımı	Var	19	30
Oral antidiyabetik	Var	33	52
Hipertansiyon	Var	30	47
Böbrek Yetmezliği	Var	3	4,7
Diyaliz	Var	2	3
Koroner Arter Hastalığı	Var	40	62,5
Periferik Arter Hastalığı	Var	34	53
Yara Genişliği	<5cm	37	58
	≥5cm	27	42
Etkilenen Ayak	Sağ	40	62,5
	Sol	24	37,5

Diyabetik ayak enfeksiyonu ortalama 5,71 (0-30) gündür . Hastaların insülin kullanım süresi ortalama 3 yıldır. 10 (%16) hastanın derin doku kültüründe üreyen mikroorganizmalar ise 3 hastada *Klebsiella pneumoniae*, 1 hastada *Klebsiella oxytoca*,2 hastada Metisiline dirençli

Staphylococcus aureus, 2 hastada *Morganella morganii*, 2 *Serratia marcescens* tespit edildi. Laboratuvar değerleri Tablo 2 de gösterilmiştir. Hastalara uygulanan monoterapi antibiyotikler sırasıyla en sık Tigesiklin (yükleme 100 mg) 2X1 IV %28, Ampisilin sulbaktam 3 g 4x1 IV, Moxifloksasin 4000 mg1x1 tablet yada IV formuydu.

Tablo 2. Hastaların Laboratuvar Bulgularının İncelenmesi

Değişkenler	Minimum	Maximum	Ortalama	Standart Sapma
Lökosit (4-10x10^{3}µL)	3700	26300	11829,6	5975,9
Hemoglobin (11-17 gr/L)	8,1	16,4	11,3	1,8
Sedimantasyon (0-20mm/saat)	7,0	136,0	63,7	35,2
CRP (0-5 mg/d/L)	0,30	1017,00	23,5	126,4
Prokalsitonin (0,05 µg/L)	0,10	7,00	1,6	2,5
Total Kolesterol (0-199 mg/dL)	92,0	270,0	172,4	49,2
Trigliserid (50-149 mg/dL)	62	165	114,8	33,2
LDL (0-99 mg/dL)	49,4	200,0	126,5	50,5
HDL (40-60 mg/dL)	24,0	83,0	36,8	14,3
HbA1c (%4,7-5,6)	6,1	11,5	8,0	3,1

Hastaların 29‘una bilateral alt extremite arteriyel ve venöz Doppler ultrasonograf yapıldı. 9’unda (%31) post stenotik monofazik akım paterni izlendi. 3’ünde (%10) aterosklerotik kontur düzensizlikleri tespit edildi. Bunlardan 3’ünda (%34) tibial arter, 2'inde (%22) popliteal arter, 2'inde (%22) derin peroneal arter ve 2'sinde (%22) derin femoral ve dorsalis pedis arter tutulumu vardı. Çalışmaya dahil edilen hastalarımızın ortalama hastaneye yatış süresi 12,7 (2-49) gün saptanmıştır. Erkek hastaların hemoglobin düzeyi ile HbA1c düzeyi, kadın hastalara göre istatistiksel olarak anlamlı daha yüksek saptandı ($p<0,05$). 5 kişiye (%8) ampütasyon uygulandı. Hastaların 23’ü (%36) şifa ve 41’i (%64) sevk edildi.

Tablo 3. Ölçek Sınıflandırmaları

Ölçekler	İyileşenler n=64 (%)	Ampüte olanlar n=64 (%)
SINBAD sınıflaması		
Düşük 0-2	35	0
Orta 3-4	19	0
Yüksek 5-6	10	5
PEDİS sınıflaması		
Enfekte olmayan	13	0
Hafif Derecede Enfeksiyon	19	0
Orta Derecede Enfeksiyon	23	0
Şiddetli Derecede Enfeksiyon	10	5

TARTIŞMA

Küresel diyabetik ayak ülserlerinin prevalansı yaklaşık %6,3'tür (9). Diyabetin en ciddi ve maliyetli komplikasyonlarından biridir. Toplamda, diyabetik hastaların %25'i yaşamları boyunca ayak ülseri geliştirir. Diyabetik ayak enfeksiyonlu (DAE) hastaların yaklaşık %50'sinin ayak enfeksiyonlarından muzdarip olduğu tahmin edilmektedir (10). Diyabet tanısı alan hastaların ilk 1 yılda ülser geliştirme insidansı 12.4% olarak saptanmış. Prospektif bir kohort çalışması, Diyabetik ayak ülserleri tehlikesinin diyabet süresi uzadıkça arttığını göstermiştir (11). Çalışmamızda da 40 yaş üzeri hastalarda diabetik ayak ülserleri mevcuttu.Ayak ülseri olan diyabetik hastaların %60'ından fazlası erkektir. Erkeklerin daha fazla açık havada çalışma, ayak bakımına zayıf uyum ve yaşam tarzlarında cinsiyete bağlı farklılıklar ile açıklanabileceği belirtilmiş (12). Çalışmamızda diyabetik ayak enfeksiyonu olarak tanımlanmış erkek hasta oranı (%67) kadınlardan belirgin olarak fazla bulunmuştur.

Diyabetik ayak ülserinin anatomik yerleşimi, yara derinliği, ayak lezyonunun enfeksiyon ve iskemisi gibi özelliklerinin yanı sıra glisemik yönetimin tümü sonucu etkiler.

Vella ve ark. başlangıçtaki HbA1c'nin DAE sonucunu tahmin etmediğini, ancak daha düşük HbA1c'ye sahip olanların daha kısa iyileşme süresine sahip olduğunu bulmuştur (13). Noel ve ark. HbA1c'si %8'in altında olan hastalardaki daha büyük yaraların, HbA1c'si %8'in üzerinde olan hastalardaki daha küçük yaralardan daha iyi iyileştiğini kaydetmiştir (14). HbA1c düzeyleri %7 veya altında olan ve değerleri çalışma boyunca artan katılımcılar paradoksal olarak daha iyi uzun vadeli iyileşme yaşadılar (15). Çalışmamızda HbA1C düzeyi %8 olarak tespit edilmiştir.

Alt ekstremite Doppler ultrasonografisinde arter lümen tıkanıklığı saptanan 9'unda (%31) mevcuttu. DM popliteal, anterior tibial, peroneal ve posterior tibial arterlerin tutulumu ile diz altında daha şiddetli periferik arter hastalık ile bağlantılıdır (16). Çalışmamızda tibial arterlerin en çok tıkanan arterler olduğu dikkati çekmiştir.

Enfeksiyon erken saptanıp zamanında kontrol altına alınmazsa yüzeysel dokudan kemik ve eklem gibi derin yapılara yayılabilir. Klinisyenler çoğunlukla, mikrobiyal kültür sonucu elde edilmeden önce ilk antibiyotikleri ampirik olarak kullanmak zorundadır. DAE'nun yanlış teşhisi, gereksiz yere aşırı veya yanlış antibiyotik kullanımına yol açar. Ayrıca, geniş spektrumlu antibiyotiklerin yaygın kullanımı ve antibiyotik direnç genlerindeki varyasyonlar nedeniyle, DAI'nin patojen türleri ve ilaç direnç oranı önemli ölçüde artmaktadır (17).

Ülkemizde yapılan bir çalışmada Gram negatif bakterilerinin tüm izolatların %60,2'sini oluşturduğunu göstermiştir (18). Ertuğrul ve ark.'nın 2017 yılında yaptıkları bir çalışmada 5 yıllık dönemlerde S. aureus izolasyon oranı %29'dan %18'e gerilemiştir. Son yıllarda DAE'den S. aureus izolasyon oranını %10 ve daha altında bildiren çalışmalar yapılmıştır (19,20). Çalışmamızda 10 (%16) hastanın derin doku kültüründe 8'i (%80) Gram pozitif, 2'si (%20) Gram negatif bakteri diğer çalışmalar ile uyumlu olduğu görüldü.

Klebsiella spp ülkemizde ve dünyadaki bir çok çalışmada gram negati bakteriler ön plana çıkmaya başlamış ve klebsiella spp ilk sıralamada hızla ilerlemektedir. DAE'larda biyofilm oluşumu, antibiyotik direncinin gelişmesinde önemli bir rol oynar(21). Farklı coğrafi bölgeler, DFU'lar üzerinde farklı bir bakteri dağılımına sahipti ve sosyoekonomik düzey, iklim koşulları, hijyen ve ayakkabı kullanımı ile ilişkilendirilebilir.

Hastanede kalış süresi ortalama 12,7 (2-49) gün olduğunu gözlemledik. Ülkemizdeki ve diğer çalışmalardan kısa süreli olmamızın nedeni ise; dal hastanesi olmamız ve diğer çok merkezli hastanelere 41'nin (%64) sevk edilmesidir (22,23).

Orta veya şiddetli diyabetik ayak enfeksiyonlarının yaklaşık %20'si küçük veya büyük amputasyona yol açar (24).Çalışmamızda 5 kişiye (%8) ampütasyon uygulandı.

Doğru ayak bakımı davranışı ve uygulaması, ayak sağlığını korumayı ve bir sağlık uzmanı tarafından yapılan düzenli ayak muayeneleri oluşabilecek yaralar için erken koruma sağlayabilir (25).

Diyabetik ayak enfeksiyonlarında; uygun olmayan ayakkabı kullanımı ve çorapsız ayakkabı giyilmesine bağlı travma, ayakların yıkandıktan sonra kurulanmaması sonucunda nemli ve ıslak ortamda mikroorganizmaların çoğalması, ayak hijyeninin yetersiz olması ve diyabet hastalarının bu konuda bilinçsiz olması risk nedenleri arasında olabileceği düşüncesindeyiz.

SONUÇ

Diyabetik ayak ülserlerinin uygun şekilde değerlendirilmesi ile İnfeksiyona bağlı morbidite, hastaneye yatış, hastanede kalış süresi ve major ekstremite ampütasyonu oranları azaltılabilmektedir. DAE gelişen hastalarda da uygun antibiyoterapi ve erken tedavi yaklaşımı amputasyonların engellenmesi açısından çok önemlidir. Hızlı ve uygun antimikrobiyal tedavi için, bölgesel verilerin paylaşılması , ülkemizdeki etken mikroorganizmaların saptanması ve doğru ampirik antimikrobiyal tedavinin belirlenmesi açısından gereklidir.

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Yazar Katkıları

Çalışma Konsepti / Tasarımı	**:** SDK, PÖ, GE, YUK
Veri toplama	**:** SDK, PÖ, GE, YUK
Veri Analizi / Yorumlanması	**:** SDK, PÖ, GE, YUK
Taslak Yazımı	**:** SDK, PÖ, GE, YUK
Teknik Destek / Malzeme Desteği	**:** SDK, PÖ, GE, YUK
İçeriğin eleştirel incelemesi	**:** SDK, PÖ, GE, YUK
Literatür Taraması	**:** SDK, PÖ, GE, YUK

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Toxoplasma Gondii, Rubella Ve CMV Seroprevalansı: Beş Yıllık Sonuçların Değerlendirilmesi

Toxoplasma Gondii, Rubella And CMV Seroprevalance: An Assessment Of Five-Year Results

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Özet

Giriş: Toxoplasma gondii, insanlar da dahil olmak üzere hemen hemen tüm sıcakkanlı hayvanları enfekte eden ve en başarılı ökaryotik patojenlerden biri olarak kabul edilen bir protozoon parazittir. Dünya çapındaki insan popülasyonunun yaklaşık %30'u kronik olarak T. gondii ile enfektedir. İlk olarak 1962'de hücre kültüründen izole edilen kızamıkçık virüsü, tek sarmallı pozitif polariteli RNA genomu içerir. Kızamıkçık virüsü, Togaviridae familyasına aittir ve Rubivirüs cinsinin tek üyesidir. Kızamıkçık hastalığının veya sözde "Alman kızamığı" nın etken maddesidir. İnsan herpesvirüs ailesinin beşinci üyesi olan Sitomegalovirüs (CMV), klinik hastalığa neden olduğu bilinen en büyük virüslerden biridir. İnsan herpesvirüsleri 6A, 6B ve 7 ile birlikte beta-herpesvirüs alt ailesine ait çift sarmallı bir DNA virüsüdür.
Amaç: İntrauterin enfeksiyonlara neden olan ve benzer klinik tablolar oluşturan Toxoplasma gondii, Rubella, CMV ve Herpes Simplex virüsünün neden olduğu konjenital enfeksiyonlar kompleksine TORCH sendromu adı verilmektedir. Biz çalışmamızda Gaziantep Halk Sağlığı Laboratuvarında Ocak 2018 - Haziran 2023 tarihleri arasında Toxoplasma gondii, Rubella ve CMV seroprevalansını tespit etmeyi amaçladık.
Yöntem: Çalışmamızda 1 Ocak 2018 ve 13 Haziran 2023 tarihleri arasında, birinci basamak sağlık kuruluşlarına çeşitli nedenlerle başvuran ve Rubella, CMV ve Toksoplazma için IgM ve IgG antikor testleri istenilen hastalara ait sonuçlar, Gaziantep Halk Sağlığı Laboratuvarı bilgi yönetim sisteminden geriye dönük olarak incelenmiştir.
Bulgular: Toxoplazma IgG antikor testi yapılan olgu sayısı 155 615, pozitif saptanan olgu sayısı 66 925 (%43.00) olarak saptandı. Toxoplazma IgM antikor testi yapılan olgu sayısı 226 874, pozitif saptanan olgu sayısı 5869 (%2.58) olarak saptandı. Rubella IgG antikor testi yapılan olgu sayısı 150 261, pozitif saptanan olgu sayısı 136 773 (%91.02) olarak saptandı.Rubella IgM antikor testi yapılan olgu sayısı 218 384, pozitif saptanan olgu sayısı 1488 (%0.68) olarak saptandı. CMV IgG antikor testi yapılan olgu sayısı 148 071, pozitif saptanan olgu sayısı 147 101 (%99.34) olarak saptandı.CMV IgM antikor testi yapılan olgu sayısı 216 972, pozitif saptanan olgu sayısı 2278 (%1.04) olarak saptandı.
Sonuç: TORCH sendromunu oluşturan hastalıklar daha çok fetüs ve yenidoğanda konjenital enfeksiyonlar yaptıkları için dünyada ve ülkemizde genellikle gebelerde epidemiyolojik çalışmalar yapılmıştır. Bizim çalışmamızın ise genel populasyonda yapılması ve olgu sayısının yüksek olması nedeniyle bu konuda literatüre ek katkı sağlayacağını umuyoruz.

Anahtar Kelimeler: Toxoplasma Gondii, Rubella, CMV, Seroprevalans.

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Abstract

Introduction: Toxoplasma gondii is a protozoan parasite that infects almost all warm-blooded animals, including humans, and is considered one of the most successful eukaryotic pathogens. About 30% of the human population worldwide is chronically infected with T. gondii. Rubella virus, first isolated from cell culture in 1962, contains a single-stranded positive-sense RNA genome. Rubella virus belongs to the Togaviridae family and is the only member of the Rubivirus genus. It is the causative agent of rubella disease, or the so-called "German measles". Cytomegalovirus (CMV), the fifth member of the human herpesvirus family, is one of the largest viruses known to cause clinical disease. It is a double-stranded DNA virus belonging to the beta-herpesvirus subfamily along with human herpesviruses 6A, 6B, and 7.
Aim: The complex of congenital infections caused by Toxoplasma gondii, Rubella, CMV and Herpes Simplex viruses, which cause intrauterine infections and create similar clinical pictures, is called TORCH syndrome. In our study, we aimed to determine the seroprevalence of Toxoplasma gondii, Rubella and CMV between January 2018 and June 2023 in Gaziantep Public Health Laboratory.
Method: In our study, the results of patients who applied to primary health care institutions for various reasons and were asked for IgM and IgG antibody tests for Rubella, CMV and Toxoplasma between January 1, 2018 and June 13, 2023, were retrospectively analyzed from the Gaziantep Public Health Laboratory information management system.
Results: The number of cases with Toxoplasma IgG antibody test was 155 615, and the number of positive cases was 66 925 (43.00%). The number of cases in which Toxoplasma IgM antibody test was performed was 226 874, and the number of positive cases was 5869 (2.58%). The number of patients who underwent Rubella IgG antibody test was 150 261 and the number of positive patients was 136 773 (91.02%). The number of patients who underwent Rubella IgM antibody test was 218 384, and the number of positive patients was 1488 (0.68%). The number of patients who underwent CMV IgG antibody test was 148 071, and the number of patients who were found positive was 147 101 (99.34%). The number of patients who underwent CMV IgM antibody test was 216 972, and the number of positive cases was 2278 (1.04%).
Conclusion: Since the diseases that make up TORCH syndrome mostly cause congenital infections in fetus and newborn, epidemiological studies have been carried out in pregnant women in the world and in our country. We hope that our study will make an additional contribution to the literature on this subject, since it was conducted in the general population and the number of cases was high.

Keywords: Toxoplasma Gondii, Rubella, CMV, Seroprevalence.

GİRİŞ

Toxoplasma gondii, insanlar da dahil olmak üzere hemen hemen tüm sıcakkanlı hayvanları enfekte eden ve en başarılı ökaryotik patojenlerden biri olarak kabul edilen bir protozoon parazittir (1). Dünya çapındaki insan popülasyonunun yaklaşık %30'u kronik olarak T. gondii ile enfektedir (2). İnsan enfeksiyonları öncelikle canlı doku kistleri içeren az pişmiş veya çiğ etin yenilmesi veya T. gondii ookistleri ile kontamine olmuş yiyeceklerin yenilmesi veya suyun içilmesiyle elde edilir (3). Erişkinlerdeki birincil enfeksiyonlar çoğunlukla asemptomatiktir, ancak bazı hastalarda lenfadenopati veya oküler toksoplazmoz görülebilir (4). Bazı izolatlarla enfekte olduğunda, bağışıklığı yeterli bireylerde şiddetli akut, yayılmış toksoplazmoz oluşabilir (5). Bağışıklığı baskılanmış kişilerde gizli bir enfeksiyonun yeniden aktivasyonu ölümcül toksoplazmatik ensefalit, miyokardit ve pnömoniye neden olabilir (6). Bağışıklığı baskılanmış hastalar ayrıca birincil enfeksiyonu veya kronik enfeksiyonun yeniden aktivasyonunu takiben ciddi hastalık riski altındadır (7). Hamilelik sırasında edinilen enfeksiyon, fetüste uzun süreli sekel, ölü doğum veya fetal ölüm gibi ciddi hasara neden olabilir (8).

İlk olarak 1962'de hücre kültüründen izole edilen kızamıkçık virüsü, tek sarmallı pozitif polariteli RNA genomu içerir (9,10). Kızamıkçık virüsü, Togaviridae familyasına aittir ve Rubivirüs cinsinin tek üyesidir. Kızamıkçık hastalığının veya sözde "Alman kızamığı" nın etken maddesidir. Çoğu enfeksiyon vakası hafif, kendi kendini sınırlayan kızamık benzeri bir

hastalığa yol açsa da, gerçek tehdit, kızamıkçık virüsü fetüsü enfekte ettiğinde ortaya çıkar (11). Özellikle enfeksiyonun düşük veya konjenital kızamıkçık sendromuna (KRS) yol açabileceği ilk üç aylık dönemde bu durum daha da önem kazanır. KRS'de kızamıkçık virüsü plasentayı enfekte edebilir, fetüse yayılabilir ve organ oluşumuna müdahale ederek ve sistemik inflamasyona neden olarak çoklu fetal sistemlerin işlevini değiştirebilir (12). KRS ile ilişkili kalıcı enfeksiyon da vardır. KRS ve Fuchsüveit sendromu(FUS) tanısı alan 28 yaşındaki bir hastanın aköz hümöründe kızamıkçık virüsü RNA'sının saptanması enfeksiyonun uzun sürebileceğini doğrulamaktadır (13).

İnsan herpesvirüs ailesinin beşinci üyesi olan Sitomegalovirüs (CMV), klinik hastalığa neden olduğu bilinen en büyük virüslerden biridir. İnsan herpesvirüsleri 6A, 6B ve 7 ile birlikte beta-herpesvirüs alt ailesine ait çift sarmallı bir DNA virüsüdür. CMV ilk olarak 1965 yılında sağlıklı bireylerde enfeksiyöz mononükleoz benzeri bir hastalık ile ilişkilendirilmiştir (14). Şu anda, sağlıklı konakçılarda asemptomatik enfeksiyondan, transplant alıcıları gibi bağışıklığı baskılanmış bireylerde ciddi ve hatta ölümcül hastalığa kadar çok çeşitli klinik sendromlara neden olduğu bilinmektedir (15).Amerika Birleşik Devletleri'nde yapılan bir araştırma, genel CMV seroprevalans oranının %50,4 olduğunu bildirdi. Prevalans yaşla birlikte artar; 1-5 yaş arası çocuklarda %20,7 kadar düşük olabilir, ancak gelişmekte olan ülkelerde yaşlı erişkinlerde %100'e yaklaşmaktadır (16).Bağışıklığı yeterli sağlıklı konakta primer CMV enfeksiyonu genellikle asemptomatiktir, ancak spesifik olmayan ateşli bir hastalık veya ateş, lenfadenopati ve lenfositoz ile karakterize enfeksiyöz mononükleoz benzeri bir sendrom olarak da ortaya çıkabilir (17). Kendi kendini sınırlayan bir seyrin ardından CMV, virüsün çoğalabileceği ve periferik monositler ve dolaşımdaki endotel hücreleri tarafından ulaşılabilecek şekilde taşınabileceği endotel hücreleri, epitel hücreleri, düz kas hücreleri ve fibroblastlar dahil olmak üzere çok çeşitli hücrelerde latent enfeksiyon oluşturur (18). İlk enfeksiyon, CMV'ye özgü IgM'nin ve daha sonra ömür boyu devam eden IgG antikorunun üretilmesine yol açar (19).

İntrauterin enfeksiyonlara neden olan ve benzer klinik tablolar oluşturan Toxoplasma gondii, Rubella, CMV ve Herpes Simplex virüsünün neden olduğu konjenital enfeksiyonlar kompleksine TORCH sendromu adı verilmektedir. Biz çalışmamızda Gaziantep Halk Sağlığı Laboratuvarında Ocak 2018 - Haziran 2023 tarihleri arasında Toxoplasma gondii, Rubella ve CMV seroprevalansını tespit etmeyi amaçladık.

YÖNTEM

Bu çalışma Uluslararası Helsinki Bildirgesi (Declaration of Helsinki) prensiplerine uygun yapılmıştır. Çalışmamızda 1 Ocak 2018 ve 13 Haziran 2023 tarihleri arasında, birinci basamak sağlık kuruluşlarına çeşitli nedenlerle başvuran ve Rubella, CMV ve Toksoplazma için IgM ve IgG antikor testleri istenilen hastalara ait sonuçlar, Gaziantep Halk Sağlığı Laboratuvarı bilgi yönetim sisteminden geriye dönük olarak incelenmiştir.Testler için, bu yıllar arasında tekrarlayan sonuçlar çalışma dışı bırakılmış, 5 yıllık süre içinde aynı hastaya ait yalnızca tek bir test sonucunun çalışmada yer alması sağlanmıştır. Tekrarlanan hasta sonuçlarının çalışmadan çıkarılması için Microsoft Excel-2010 programı ile bir sorgulama yapılmış ve tekrarlanan sonuçlar çalışmaya alınmamıştır. Testler; elektrokemilüminesans immünoassay (Cobas e601, Roche Diagnostic GmbH, Germany) yöntemleri ile üretici firma talimatları doğrultusunda çalışılmıştır. Cihazlarda kullanılan kitlerin prospektüslerinde belirtilen referans aralıklarına göre Toxoplazma IgG, IgM, Rubella IgG, IgM, CMV IgG, CMV IgM antikor testlerinde; Cobas e601 için >1.0 COI olan sonuçlar pozitif olarak kabul edilmiştir. Verilerin analizi IBM SPSS 25.0 istatistik paket programı kullanılarak yapılmıştır. Her bir test için, 2018-2023 yılları arasında pozitiflik saptanan hasta sayılarının dağılımları

belirlenmiş, kategorik değişkenler için frekans ve yüzdeler gösterilmiştir. İstatistiksel analizler SPSS versiyon 25 yazılımı kullanılarak yapıldı. P <0.05' in altında olduğu durumlar istatistiksel olarak anlamlı sonuçlar şeklinde değerlendirildi.

BULGULAR

Toxoplazma IgG antikor testi yapılan olgu sayısı 155 615, pozitif saptanan olgu sayısı 66 925 (%43.00) olarak saptandı. Toxoplazma IgM antikor testi yapılan olgu sayısı 226 874, pozitif saptanan olgu sayısı 5869 (%2.58) olarak saptandı. Rubella IgG antikor testi yapılan olgu sayısı 150 261, pozitif saptanan olgu sayısı 136 773 (%91.02) olarak saptandı. Rubella IgM antikor testi yapılan olgu sayısı 218 384, pozitif saptanan olgu sayısı 1488 (%0.68) olarak saptandı. CMV IgG antikor testi yapılan olgu sayısı 148 071, pozitif saptanan olgu sayısı 147 101 (%99.34) olarak saptandı. CMV IgM antikor testi yapılan olgu sayısı 216 972, pozitif saptanan olgu sayısı 2278 (%1.04) olarak saptandı.

Toxoplazma IgG antikor testi yapılanların 16 900' ü erkek, 138 715' i kadın olguydu. Erkek olguların 6416'sı pozitif (%37.96), 10 484'ü negatif (%62.04) olarak saptandı. Kadın olguların 60 509'u pozitif (%43.62), 78 206'sı negatif (%56.38) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%26.12), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %2.02 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %0.74 olarak tespit edildi.

Toxoplazma IgM antikor testi yapılanların 18 248'i erkek, 208 626'sı kadın olguydu. Erkek olguların 347'si pozitif (%1.90), 17 901'ü negatif (%98.1) olarak saptandı. Kadın olguların 5522'si pozitif (%2.64), 203 104'ü negatif (%97.36) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%1.36), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %0.07 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %0.02 olarak tespit edildi.

Rubella IgG antikor testi yapılanların 16 865'i erkek, 133 396'sı kadın olguydu. Erkek olguların 15 861'i pozitif (%94.03), 1007'si negatif (%5.96) olarak saptandı. Kadın olguların 120 922'si pozitif (%90.64), 12 474'ü negatif (%9.35) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%47.75), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %4.78 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %0.79 olarak tespit edildi.

Rubella IgM antikor testi yapılanların 17871'i erkek, 200 513'ü kadın olguydu. Erkek olguların 160'ı pozitif (%0.89), 17 711'si negatif (%99.1) olarak saptandı. Kadın olguların 1328'i pozitif (%0.66), 199 185'i negatif (%99.33) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%0.38), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %0.02 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %0.01 olarak tespit edildi.

CMV IgG antikor testi yapılanların 18 710'u erkek, 129 361'i kadın olguydu. Erkek olguların 18 368'i pozitif (%98.06), 362'si negatif (%1.93) olarak saptandı. Kadın olguların 128 753'ü pozitif (%99.52), 608'i negatif (%0.47) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%51.46), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %5.71 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %1.01 olarak tespit edildi.

CMV IgMantikor testi yapılanların 20 293'ü erkek, 196 679'u kadın olguydu. Erkek olguların 386'sı pozitif (%1.90), 19 907'si negatif (%98.09) olarak saptandı. Kadın olguların 1892'si

pozitif (%0.96), 194 787'si negatif (%99.03) olarak saptandı. Toplam olgular içerisinde en yüksek pozitiflik oranı 25-44 yaş kadınlara aitti (%0.52), 25-44 yaş aralığı erkeklerde ise pozitiflik oranı %0.08 olarak bulundu. Geriatrik yaş grubunda (65+) pozitiflik oranı %0.01 olarak tespit edildi.

TARTIŞMA

Ülkemizde 2009 yılında yapılan bir çalışmada 1972 hamile kadının 952'sinde (%48.3) anti-toksoplazma IgG antikoru seropozitifliği bulunurken, test edilen deneklerin 8'inde (%0.4) yalnızca anti-Toksoplazma IgM antikoru pozitif bulundu. Gebelerin 1896'sında (%96.1) anti-rubella IgG pozitifliği, 4'ünde (%0.2) anti-rubella IgM pozitifliği saptanmıştır. Gebelerin 1900' ünde (%96.4) anti-CMV IgG pozitifliği, 13'ünde (%0.7) anti-CMV IgG pozitifliği saptandı (20). Bizim çalışmamızda IgM antikor düzeyleri bu çalışmaya göre her 3 hastalık için daha yüksek saptanmıştır.

Ülkemizde 274 gebe hasta üzerinde yapılan TORCH seroprevalans çalışmasında Toxoplasma gondii IgM ve IgG antikorları sırasıyla 8 (%2.9) ve 65 (%23.7), Rubella IgM ve IgG antikorlarının pozitifliği sırasıyla 2 (%0.7) ve 233 (%98.3) olarak saptanmıştır (21). Bizim çalışmamızda hem Rubella hem de Toxoplasma IgG ve IgM düzeyleri bu çalışmaya kıyasla düşük saptanmıştır.

Genel olarak dünyadaki insan nüfusunun yaklaşık %25 ila 30'unun Toksoplazma ile enfekte olduğu varsayılmaktadır. Aslında, yaygınlıklar ülkeler arasında (%10'dan %80'e kadar) ve genellikle belirli bir ülke içinde veya aynı bölgedeki farklı topluluklar arasında büyük farklılıklar göstermektedir (22).

Kuzey Amerika, Güney Doğu Asya, Kuzey Avrupa ve Afrika'nın Sahel ülkelerinde düşük seroprevalanslar (%10 ila %30) gözlenmiştir. Orta ve Güney Avrupa ülkelerinde orta düzeyde yaygınlıklar (%30 ila %50) ve Latin Amerika ve tropik Afrika ülkelerinde yüksek yaygınlıklar bulunmuştur. Bizim çalışmamızda Toxoplazma IgG antikor testi yapılan olgu sayısı 155 615, pozitif saptanan olgu sayısı 66 925 (%43.00) olarak saptandı. Ülkemizdeki bu oran Güney Avrupa ülkelerindeki seroprevalans oranlarına benzerdi.

Nemli ve ılıman bir iklime sahip tropik ülkelerde klasik olarak daha yüksek prevalanslar gözlenir ve bunun tersine, kurak ülkeler veya daha soğuk ülkelerde daha düşük prevalanslar bulunur, ancak antropojenik faktörler, beslenme alışkanlıkları da dahil olmak üzere insan seroprevalansındaki varyasyonların büyük bir bölümünü açıklar. Örneğin etin pişirilmesi, ellerin yıkanması, tüketilen et veya sebze çeşitleri ve sebze temizliği, ekonomik, sosyal veya kültürel alışkanlıklar, su kalitesi ve sanitasyon kapsamı. Seroprevalans yaşla birlikte artar, ancak yaşa bağlı olarak enfeksiyonun bulaşma oranı ülkeye ve sosyoekonomik düzeye göre değişir. Yetersiz hijyen koşullarında yaşayan popülasyonlarda çocukluk çağında maksimuma yakın seroprevalansa ulaşılabilir, muhtemelen oosit alımıyla tellürik veya su kaynaklı kontaminasyonla bağlantılıdır. Bu, insanların tüketim için filtrelenmemiş yüzey sularını kullandığı alanlarda ve muhtemelen aynı zamanda, örneğin rekreasyon için tatlı su ile temasın olduğu alanlarda, suyun önemli bir insan enfeksiyonu kaynağı olduğuna işaret etmektedir (23, 24). Ülkemizin farklı bölgelerinde yapılan çalışmalarda birbiriyle çelişen seroprevalans sonuçlarının olmasının temel sebepleri de bu çevresel ve sosyoekonomik etkenlerdir.

Örnek olarak, kuzey Rio de Janeiro eyaletinde (Brezilya) bulunan bir şehirde yaşa göre düzeltilmiş seroprevalans, daha düşük sosyoekonomik düzeydeki grup için %84 iken, orta ve üst sosyoekonomik düzeylerdeki gruplar için sırasıyla %62 ve %23'tür (25). Alt sosyoekonomik düzeydeki popülasyondaki çoğu kişi (%84'e kadar) 15 yaşında enfekte

olurken, üst sosyoekonomik düzeydeki popülasyonda enfeksiyon çoğunlukla 20 yaşından sonra kazanılmıştır (20 ila 29 yaş grubu için yaklaşık %20, 40 ila 49 yaş grubu için %70). Çok değişkenli bir risk faktörü analizinde, bu, filtrelenmemiş su sağlanan alanlarda yaşayan en fakir nüfusla birlikte su kaynağındaki farklılıklara bağlandı. Sosyoekonomik seviyelere göre bu farklı Toksoplazma edinme modelleri, az gelişmiş tropikal ülkelerde daha alakalı olabilir, ancak Amerika Birleşik Devletleri'nde (ABD) Toksoplazma enfeksiyonu da yoksullukla ilişkili bir enfeksiyon olarak kabul edildi (26). Genel seroprevalans (ABD ve yabancı uyruklu bireyler birlikte), Hispanik olmayan siyah kişilerde ve Meksikalı Amerikalılarda İspanyol olmayan beyaz kişilere göre daha yüksekti (27). Bizim çalışmamızda da vakaların tamamı göz önüne alındığında toxoplazma IgM ve IgG seroprevalansı 25-44 yaş aralığında en yüksek olarak bulundu (sırasıyla %1.36 ve %26.14). İkinci sıklıkta görülen toxoplazma IgM ve IgG seroprevalans yaş aralığı 15-24' tü (sırasıyla %1.04 ve %10.9). Bizim çalışmamızda olguların sosyoekonomik durumları ile ilgili veri mevcut değildi.

Mantıksal olarak, artan sosyoekonomik düzeyler, hijyenik koşulların iyileştirilmesi, çiftçilik sistemlerindeki değişiklikler, dondurulmuş et tüketimi ve kedilerin sterilize edilmiş gıdalarla beslenmesi ile birlikte, son zamanlarda çoğu sanayileşmiş ülkede seroprevalansta sürekli bir azalmaya yol açmıştır. Amerika Birleşik Devletleri'nde ulusal bir araştırma, 12 ila 49 yaşları arasındaki ABD doğumlu kişilerde yaşa göre ayarlanmış T. gondii yaygınlığının 1988'den 1994' e kadar %14.1'den 1999'dan 2004'e kadar %9' a düştüğünü buldu (27). Bizim çalışmamızda vakaların tamamı göz önüne alındığında 10-44 yaş aralığı toxoplazma IgG seroprevalans oranı %42.94, toxoplazma IgM seroprevalans oranı %2.55 olarak saptandı. Fransa'da gebe kadınlardaki seroprevalanslar 1960'ların başında yaklaşık %80, 1980'lerde yaklaşık %66, 1995'te %54 ve 2003'te %44 iken, aynı zamanda gebe kadınların ortalama yaşı artmıştır (28). Bu azalan seroprevalans, Avrupa'da incelendiği tüm alanlarda gözlemlenmiştir. Örneğin, Hollanda'da üreme çağındaki kadınlarda seroprevalans 1995'ten 1996'ya %35.2'den 2006'dan 2007' ye %18.5'e düşmüştür (29). Bizim çalışmamızda 25-44 yaş aralığında kadınlarda 2018 yılında toxoplazma IgG seroprevalans oranı %26.99, toxoplazma IgM seroprevalans oranı %1.35 iken 2023 yılının ilk 6 ayında bu oranlar sırasıyla %23.7 ve %1.62 olarak tespit edildi.

İnsanlar, kızamıkçık enfeksiyonu için bilinen tek rezervuardır (30). Doğum sonrası kızamıkçık, öncelikle virüs yüklü havadaki damlacıkların solunması veya enfekte nazofaringeal sekresyonlarla doğrudan temas yoluyla bulaşır (31). En yüksek enfeksiyon oranları genellikle kış sonu ve ilkbahar başında görülür (32). Kızamıkçık aşısının kullanılmaya başlanmasından önce, kızamıkçık dünya çapında endemikti, salgınlar 6 ila 9 yıllık aralıklarla meydana geliyordu ve büyük salgınlar her 10 ila 30 yılda bir meydana geliyordu (33). 1962'den 1965'e kadar olan son büyük salgın sırasında, hamile kadınların yüzde 10' u enfekteydi ve enfekte annelerden doğan bebeklerin %30'u nihayetinde konjenital kızamıkçık sendromu belirtileri gösterdi (34).

Yalnızca Amerika Birleşik Devletleri' nde, 13.000'den fazla fetal veya erken bebek ölümüyle birlikte en az 12.5 milyon klinik olarak edinilmiş kızamıkçık vakası vardı. Yine bu ülkede 1962'den 1965'e kadar olan pandemi sırasında 20.000 konjenital kızamıkçık sendromu vakası görüldü. 1969'da canlı zayıflatılmış kızamıkçık aşısının piyasaya sürülmesinden bu yana, kızamıkçık Kuzey Amerika'da ve birçok gelişmiş ülkede giderek daha nadir hale geldi (35).Aşılamanın başlamasından sonra 1969'dan 1989'a kadar yıllık kızamıkçık vakası ABD'de bildirilen kızamıkçık vakalarının sayısı %99.6 ve rapor edilen yıllık konjenital kızamıkçık sendromu vakalarının sayısı %97.4 azaldı (34). 1998'den 2000'e, 2001'den 2004'e ve 2005'ten 2011' e ABD' de yıllık vaka sayıları sırasıyla 272, 13 ve 11 idi (36). 29 Nisan 2015' de Pan

Amerikan Sağlık Örgütü kızamıkçığın Amerika bölgesinin tamamında ortadan kaldırıldığını resmen ilan etti (37).

Günümüzde, gelişmiş ülkelerdeki kızamıkçık vakaları çoğunlukla "ithal" ediliyor. Bu ithalat kızamıkçığın endemik olduğu ve çoğunlukla eksik aşılanmış veya aşılanmamış bireyler yoluyla olmaktadır (38). Bizim çalışmamızda ise 2018 yılında rubella IgG seroprevalans oranı %90, rubella IgM seroprevalans oranı %0.59 iken, 2023 yılının ilk 6 ayında bu oranlar sırasıyla %90.5 ve %0.49 olarak tespit edilmiştir. Bu durum bize yaklaşık 5 yıllık süreçte kızamıkçık seroprevalans oranlarında ciddi bir düşme olmadığını göstermektedir. Küresel olarak kızamıkçık oluşmaya devam ediyor ve dünya çapında, özellikle de rutin çocukluk kızamıkçık aşısının bulunmadığı veya yakın zamanda uygulanmaya başlandığı ülkelerde 100.000'den fazla vaka bildirildi (39).

2011 yılında Dünya Sağlık Örgütü (DSÖ), kızamıkçık içeren aşının ulusal aşılama programlarına dahil edilmesi için tercih edilen stratejiye ilişkin kılavuzunu güncelledi ve esas olarak 9 ay ile 14 yaş arasındaki çocukları hedefleyen bir aşılama kampanyası önerdi (40). Rutin çocukluk aşılamalarına kızamıkçık içeren bir aşı ekleyen DSÖ üyesi devletlerin sayısı 1996-2016 yılları arasında %78.4 artarak 83' den 152'ye yükselmiştir (41).

2012'den 2016'ya kadar rutin çocukluk aşılama programlarına kızamıkçık aşısını ekleyen 20 ülkenin daha olması bu konuda cesaret verici bir durumdur. Buna rağmen, dünyanın bazı bölgelerinde, hatta nüfusun önemli bir kısmının duyarlı olduğu ülkelerde bile, aralıklı kızamıkçık salgınları meydana gelmeye devam ediyor (42). Japonya'daki son kızamıkçık salgını, ilk aşılama stratejisi kızamıkçık aşısını yalnızca ergen kızlara sağladığından, birincil olarak ilk kızamıkçık aşılama programına dahil olmayan duyarlı erkeklere atfedilebilir (43). 29 Kasım 2018 itibarıyla Japonya'da 2.186 kızamıkçık vakası vardı ve vakaların %70'inden fazlası Tokyo ve çevresindeki vilayetlerde bildirildi. Bu, 7 Ekim 2018'de bildirilen 1.103 kızamıkçık vakasına göre önemli bir artış olarak değerlendirilmiştir (44). 22 Ekim 2018 itibariyle, Hong Kong'daki Sağlık Bakanlığının Sağlığı Koruma Merkezi, 2018'de iki erkek ve dört kadını etkileyen yalnızca altı yerel kızamıkçık enfeksiyonu vakası kaydetti. Bu hastaların yaşları 3 ile 65 arasında değişmekteydi (45). Bizim çalışmamızda 2018 yılında Gaziantep İli' nde tespit edilen aktif kızamıkçık vaka sayısı 177 idi. Bu vakaların 112' si 25-44 yaş aralığında ve bunların 105' i kadındı. Vakaların 43' ü 15-24 yaş aralığında, 65 yaş ve üstü vaka sayısı sadece 2 idi.

Çocuklarda kızamıkçık her iki cinsi de eşit derecede etkilerken, yetişkinlerde kızamıkçık erkeklerden çok kadınları etkiler. Aşı öncesi dönemde, kızamıkçık en yaygın olarak 5 ila 9 yaş arası çocuklarda görülüyordu (46). Bizim çalışmamızda yaklaşık 5 yıllık süreçte; 0-14 yaş aralığı erkek çocuklarda rubella IgG pozitif vaka sayısı 1577, kız çocuklarda 1654, rubella IgM pozitif erkek çocuk sayısı 5, kız çocuk sayısı 12 olarak saptandı.

Şu anda bildirilen vakaların çoğu 20 yaş ve üstü bireylerden oluşmaktadır. Kızamıkçık için risk faktörleri arasında kısmen aşılanmış veya aşılanmamış kişiler, endemik bölgelere seyahat, kızamıkçıklı aile üyelerine maruz kalma ve immün yetmezlik yer alır (47). Bizim çalışmamızda da kızamıkçık için seroprevalans oranları en sık 25-44 yaş aralığındaydı. Fakat kadınlardaki seroprevalans oranları (rubella IgG için %90.64 ve rubella IgM için %0.66) erkeklere göre (rubella IgG için %94.03 ve rubella IgM için %0.89) literatürün aksine daha düşük olarak tespit edilmiştir.

Herpesvirüs ailesinin (Herpesviridae) bir üyesi olan CMV, dünya çapında yaygın olarak görülen ve önemli sayıda kişiyi hayatlarının bir noktasında enfekte eden bir patojendir (48). ABD'de yapılan bir araştırma, genel sitomegalovirüs (CMV) seroprevalans oranının %50.4

olduğunu bildirdi. Prevalans yaşla birlikte artar; 1-5 yaş arası çocuklarda %20.7 kadar düşük olabilir, ancak gelişmekte olan ülkelerde yaşlı erişkinlerde %100' e yaklaşmaktadır (49, 50). Yine ABD' de yapılan bir çalışmada virüsün 5 yaşına kadar çocukların yaklaşık %30' unu ve 40 yaşına kadar yetişkinlerin %50' sinden fazlasını enfekte ettiği tahmin edilmektedir (51). Bizim çalışmamızda CMV IgG seropozitifliği %99.34 olarak saptandı. Bunun anlamı Türk toplumunun tamamına yakını CMV ile enfekte olmuş durumdadır. Bizim çalışmamızda 0-4 yaş aralığında CMV antikor testi yapılan vakalarda CMV IgG seroprevalansı %80.7 olarak saptandı. Yine bu yaş grubunda 104 vakaya CMV IgM testi yapıldı ve 3 vakada pozitiflik saptandı (%2.88).

CMV seroprevalans oranı; gelişmekte olan ülkelerde, ileri yaşlarda, kalabalık ve ekonomik olarak zor durumdaki popülasyonlarda en yüksektir. Bağışıklığı yeterli sağlıklı konakta primer CMV enfeksiyonu genellikle asemptomatiktir, ancak spesifik olmayan ateşli bir hastalık veya ateş, lenfadenopati ve lenfositoz ile karakterize enfeksiyöz mononükleoz benzeri bir sendrom olarak da ortaya çıkabilir (52). Bizim çalışmamızda ileri yaş kabulen edilen geriatrik yaş grubunda (65+) CMV IgM seroprevalansı %0.01, CMV IgG seroprevalansı %99.66 olarak saptandı. Bu durum ileri yaşlarda CMV seroprevalansının arttığı bilgisi ile uyumludur. Bizim çalışmamızda CMV seropozitifliği 25-44 yaş aralığında en yüksekti (CMV IgG için %57.18).

Kendi kendini sınırlayan bir seyrin ardından CMV, virüsün çoğalabileceği ve taşınabileceği endotel hücreleri, epitel hücreleri, düz kas hücreleri ve fibroblastlar dahil olmak üzere çok çeşitli hücrelerde aktif enfeksiyon oluşturur (53). İlk enfeksiyon, CMV'ye özgü IgM'nin ve daha sonra ömür boyu devam eden IgG antikorunun üretilmesine yol açar (54).Genel olarak, CMV seroprevalansı kadınlarda, sosyoekonomik düzeyi düşük kişilerde ve gelişmekte olan ülkelerde daha yüksektir. Özellikle üreme çağındaki kadınlar arasında, küresel CMV seroprevalansı %45 ila %100 arasında değişmektedir (55).

Karşılaştırmalı olarak, Japonya, Avrupa, Latin Amerika, Kanada ve Amerika Birleşik Devletleri' nden 15 çalışma üreme çağındaki kadınlar için CMV IgG seroprevalans tahminleri bildirdi. Japonya' da seroprevalans %60.2 olarak bildirildi (56). Avrupa ve Latin Amerika bölgelerindeki gelişmekte olan ülkelerde, üreme çağındaki kadınlar arasında bildirilen CMV IgG seroprevalansları benzerdi. Meksika' da yürütülen araştırmalar, üreme çağındaki kadınlar için %58.3 ila %94.5 arasında CMV IgG seroprevalansları bildirmiştir. Avrupa' da, CMV IgG seroprevalansı, Polonya' da (57) üreme çağındaki kadınlar arasında %57.3' ten Romanya' da %95.7' ye kadar değişmektedir. Karşılaştırıldığında, Avrupa' nın gelişmiş ülkelerinde üreme çağındaki kadınlarda CMV IgG seroprevalansı %45.6 ile %65.9 arasında değişmektedir (58).

Üreme çağındaki kadınlar arasındaki seroprevalans, yaşla birlikte potansiyel bir artışa işaret eder; ancak, bu bulgular küçük veri seti ile sınırlıdır. Meksika'daki gebe kadınlarda CMV enfeksiyonunun seroprevalansı 20 ila 30 yaşındakilerde, ≤ 20 yaşındakilere göre daha yüksekti (sırasıyla %91.3' e karşı %86.5). Kanada ve Amerika Birleşik Devletleri'nde yapılan çalışmalar, seroprevalansın >40 yaşındaki kadınlar arasında, ≤ 40 yaşındaki kadınlara kıyasla daha yüksek olduğunu göstermektedir. Avrupa çalışmalarında gözle görülür yaşa bağlı eğilimler tanımlanmamıştır (59, 60). Bizim çalışmamızda 25-44 yaş aralığında kadın vakalarda CMV IgG seropozitifliği %51.46 olarak tespit edildi ve bu sonuç genel literatürü teyit ediyordu. Ayrıca CMV IgM seropozitifliği yine bu yaş grubunda diğer yaş gruplarına göre en yüksek saptandı (%0.68).

IgM antikorlarının yokluğunda CMV IgG antikorlarının varlığı akut değil, önceki enfeksiyonu gösterir (61). İki çalışma, özellikle erkek popülasyonları için CMV IgG seroprevalansını bildirdi: Ulusal olarak temsili popülasyona dayalı bir örnekten alınan bir

kesitsel ankette %39.3, Fransa (Avrupa) ve Kuzey Karolina'da ikamet eden yetişkinler arasında kesitsel bir sero-anket kullanan ABD merkezli bir çalışmada %48.0 seroprevalans oranları bulunmuştur (62,63). Bizim çalışmamızda erkeklerde CMV IgG seroprevalansı %98.06 olarak tespit edilmiş olup literatür değerlerinin üzerindeydi. Erkeklerde 25-44 yaş aralığında CMV IgG seroprevalansı %7.63 olarak tespit edilmiştir.

Avrupa ve Latin Amerika'da seroprevalans %45.6 ila 95.7 (64, 65) ve Latin Amerika'da %58.3 ila 94.5 (66, 67) arasında değişen çalışmalarda benzerdi. Kuzey Amerika'da seroprevalans 24.6-%81.0 arasında değişiyordu (68, 69). CMV IgM antikorlarının varlığı, yeni bir enfeksiyonun göstergesi olabilir (yani, birincil, reaktivasyon veya yeniden enfeksiyon). Erkeklerde CMV IgM seroprevalansına ilişkin veriler içeren hiçbir çalışma tespit edilmemiştir. Üreme çağındaki kadınlar arasında, tahminler birincil ve ikincil CMV enfeksiyonu yükünün Avrupa (%1.0-4.6) ve Kuzey Amerika'da (%2.3-4.5) benzer olduğunu göstermektedir; bu seroprevalanslar Japonya' da (%0.8) ve Latin Amerika' da (%0-0.7) gözlenenlerden daha yüksekti (70). Bizim çalışmamız ise erkeklerde CMV IgM seroprevalansına ilişkin veriler içeren nadir çalışmalardandır. CMV IgM antikor testi yapılanların 20 293 erkek olgunun 386' sı pozitif (%1.90), 19 907' si negatif (%98.09) olarak saptandı.

Yetişkinler arasında, seroprevalans en geniş aralıkta Avrupa ülkelerinde (%44.4-95.7), en dar aralık ise Japon çalışmalarında gözlemlendi (%67.2-70.9). Latin Amerika ve Kuzey Amerika, sırasıyla %59.1 ila %91.3 ve %33.0 ila %81.0 aralığında seroprevalans açısından dikkate değer farklılıklara sahipti. Menzil maksimumları karşılaştırıldığında, Avrupa'nın yetişkinler arasında en yüksek CMV seroprevalansına sahip olduğu görüldü. Benzer şekilde, Avrupa'daki yaşlılar arasında, çok sayıda makale, popülasyonun yaklaşık %2'sinin CMV IgG için seronegatif olduğunu belirterek, bu bölgedeki yaşlılar arasında yüksek bir CMV seroprevalansı olduğunu düşündürmektedir (71,72). Bizim çalışmamızda 65+ olan 1501 olguda CMV IgG seronegatif olgu sayısı 5 olarak saptanmıştır (%0.33).

Belirlenen çalışmalarda bildirilen son veriler, yaş kategorileri arasında seroprevalans aralıklarında farklılıklar olduğunu ortaya koydu. Avrupa çalışmalarında, aralıkların maksimum değerleri büyük ölçüde değişmedi, ancak minimum değerler yaş aralıklarıyla arttı. Latin Amerika'dan elde edilen veriler seroprevalansın 20-30 yaş grubunda 12-20 yaş grubuna kıyasla daha yüksek olduğunu göstermiştir (%91.3' e karşı %86.5). Seroprevalansta yaşa bağlı artışlar Kuzey Amerika çalışmalarında da dikkat çekiciydi (73). CMV IgG seroprevalansı, bu raporda yer alan gelişmekte olan ülkelerde gelişmiş ülkelerden daha yüksekti. Yetişkinler arasında, CMV IgG seroprevalansı gelişmiş ülkeler için %33.0 ila %81.0 ve gelişmekte olan ülkeler için %59.1 ila %95.7 arasında değişmektedir. Yaşlılar için seroprevalans, gelişmiş ülkeler için %64.5 ila 96.2 ve gelişmekte olan ülkeler için %93.8 ila 97.7 idi (74-76). Bizim çalışmamızda ise 25-44 yaş aralığı CMV IgG seropozitiflik oranı %57.18, 15-24 yaş aralığı seropozitiflik oranı %34.57 ve 10-14 yaş aralığı seropozitiflik oranı %1.23 olarak saptanmıştır ve literatürü teyit etmiştir.

SONUÇ

TORCH sendromunu oluşturan hastalıklar daha çok fetüs ve yenidoğanda konjenital enfeksiyonlar yaptıkları için dünyada ve ülkemizde genellikle gebelerde epidemiyolojik çalışmalar yapılmıştır. Bizim çalışmamızın ise genel populasyonda yapılması ve olgu sayısının çok yüksek olması nedeniyle bu konuda literatüre ciddi katkı sağlayacağını umuyoruz.

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Yazar Katkıları

Çalışma Konsepti / Tasarımı	**:** ED, OEA, AD, GÇ
Veri Toplama	**:** ED, OEA, AD, GÇ
Veri Analizi / Yorumlanması	**:** ED, OEA, AD, GÇ
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İçeriğin Eleştirel İncelemesi	**:** ED, OEA, AD, GÇ
Literatür Taraması	**:** ED, OEA, AD, GÇ

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The Effects of miR-30a and miR-17 Biomarkers and Methylprednisolone in Experimental Spinal Cord Injury in Rats

Sıçanlarda Deneysel Omurilik Yaralanmasında miR-30a ve miR-17 Biyomarkerları ve Metilprednizolonun Etkileri

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Abstract

Introduction: Methylprednisolone, is a neuroprotective steroid with many effective mechanisms such as inflammation, cell blood flow changes, and apoptosis in the early period following spinal cord injury. This study aimed to demonstrate the inhibitory activity of methylprednisolone to prevent early injury through microRNA expressions, which are predicted to play a role in genomic regulation.
Method: This present study was conducted on 56 male Sprague-Dawley rats. All the animals divided into 8 groups which consists of 7 animals each. Laminectomy procedure was performed between levels T5-8. All the groups except the two control groups have been damaged with the Yasargil aneurysm clip for 1 minute at the T5 level. T5-8 spinal cord tissue was removed at the 6th, 12th, and 24th hours after clipping. Methylprednisolone was given to the intraperitoneal cavity only to the clipped groups. As a result of histopathological and immunohistochemical examination, there was a significant decrease in cell necrosis, edema, hemorrhage and white matter-gray matter transition in groups given methylprednisolone. Damaged spinal cord samples excised from all rats. miR-30a and miR-17 gene expression levels were evaluated by quantative PCR method.
Results: miR-30a was significantly upregulated at 12th and 24th hours after spinal cord injury and this rise was restricted in the methylprednisolone treated groups.. miR-17 was down-regulated at the 6th hour and and reached its lowest level at the 12th hour.
Conclusion: Methylprednisolone has statistically significant healing effects on spinal cord injury through the mechanism of miR-30a and miR-17.

Keywords: miRNA, Methylprednisolone, Spinal Cord Injury, miR-30a, miR-17.

Özet

Giriş: Metilprednizolon, omurilik yaralanması sonrası erken dönemde inflamasyon, hücre kan akımı değişiklikleri ve apoptoz gibi birçok etkili mekanizmaya sahip nöroprotektif bir steroiddir. Bu çalışma, genomik regülasyonda rol oynadığı tahmin edilen mikroRNA ifadeleri aracılığıyla metilprednizolonun erken hasarı önlemedeki inhibitör aktivitesini göstermeyi amaçlamıştır.
Yöntem: Bu çalışma 56 adet erkek Sprague-Dawley cinsi sıçan üzerinde yapılmıştır. Tüm hayvanlar, her biri 7 hayvandan oluşan 8 gruba ayrıldı. T5-8 seviyeleri arasında laminektomi işlemi uygulandı. İki kontrol grubu dışındaki tüm gruplara T5 seviyesinden 1 dakika süreyle Yaşargil anevrizma klipsi ile hasar verildi. Klipslemeden 6, 12 ve 24. saatlerde T5-8 omurilik dokusu alındı. Sadece kliplenen gruplara intraperitoneal kaviteye metilprednizolon verildi. Histopatolojik ve immünohistokimyasal inceleme sonucunda metilprednizolon

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verilen gruplarda hücre nekrozu, ödem, kanama ve beyaz cevher-gri madde geçişinde anlamlı azalma oldu. Tüm sıçanlardan eksize edilen hasarlı omurilik örnekleri. miR-30a ve miR-17 gen ekspresyon seviyeleri kantitatif PCR yöntemi ile değerlendirildi.
Bulgular: miR-30a, omurilik yaralanmasından sonra 12. ve 24. saatlerde önemli ölçüde yukarı regüle edildi ve bu artış metilprednizolon ile tedavi edilen gruplarda sınırlıydı. miR-17, 6. saatte aşağı regüle edildi ve 12. saatte en düşük seviyesine ulaştı.
Sonuç: Metilprednisolon, miR-30a ve miR-17 mekanizması aracılığıyla omurilik yaralanmasında istatistiksel olarak anlamlı iyileştirici etkilere sahiptir.

Anahtar Kelimeler: miRNA, metilprednizolon, omurilik yaralanması, miR-30a, miR-17.

INTRODUCTION

Spinal cord injury (SCI) is a type of injury with a high rate of disability. It can lead to harm or loss of sense and motor function but also may lead to multiple organ dysfunctions. The incidence of spinal cord injury varied between 13.019-163.420 per million people (1). The earliest records of SCI are in the 5000-year-old Edwin Smith papyrus. In these records, studies on soft tissue and bone tissue injuries following spinal trauma are described as incurable disorders, and research into the physiopathology and biomechanics of their alterations in neural tissue are ongoing (2).

The first known spinal cord injury in history has been reported in British naval hero Lord Admiral Sir Horatio Nelson (1758–1805). After a sniper shell that enters the chest and spinal cord told the surgeon, "All power of motion and feeling below my chest is gone." Mr. Beatty has confirmed that it is an incurable disorder (3).

There are different reasons of SCI, including falls, motor vehicle accidents/crashes, sports-related accidents, violence, and other remaining causes of injury. Motor vehicle accidents and falls are the most common causes of injury accounting for a nearly equal ratio (4).

In recent years, various animal models have been developed to allow an understanding of the complicated biomedical mechanisms of SCI and to advance medical strategies for this situation (5). Rodents are the mostly utilized animals in SCI studies because of their availability, ease of usage, and cost-effectiveness in comparison with primates (6). A cystic gap arises in the core of the spinal cord in the rat, cat, monkey, and human SCI, , which is surrounded by a rim of anatomically protected white matter (7). Previous studies in the literature provide evidence that rat models of SCI may be used to design and evaluate the structural and functional advantages of SCI treatment strategies (8).

MicroRNAs (miRNAs), a subset of noncoding RNAs, are endogenously launched small RNA molecules of ~22 nt (nucleotide) length.They may post-transcriptionally coordinate the division of target mRNAs or only suppress their translation (9). miRNAs create almost 1% of all estimated genes in nematodes, flies, and mammals (10, 11,12, 13). miRNAs are crucial for normal development and are associated with a wide range of biological functions. (14). Abnormal expression of miRNAs is related to many human illnesses (15, 16). Extracellular miRNAs have been widely notified as potential biomarkers for a diversity of diseases and they also serve as signal molecules to mediate intercellular communications (17, 18, 19).

miRNAs have key roles in the regulation of different processes in mammals. They provide a key and strong tool in gene arrangement and thus a potential new class of therapeutic targets. miRNAs largely exhibit limited complementarity with their target mRNAs in animals however, this is still enough to coordinate varied physiological processes. It has been suggested that they repress the initiation step of the translation process, which may be

followed by mRNA degradation (20). The functions of miRNAs such as; cell death and proliferation, regulation of developmental timing, physiological condition, neuronal cell fate, cardiomyocyte differentiation and proliferation, neural proliferation signaling, down-regulated in B cell chronic lymphocyte leukemia, upregulated in B-cell lymphoma, development and function of the immune system, insulin secretions and brain morphogenesis" have been reported in various publications (20-30).

This present study aimed to create spinal cord injury in rats and determine miRNAs specific to spinal cord injury in tissue and explain the recycling mechanism of damage in patients given methylprednisolone through miRNAs and be an example to future treatment plans.

METHOD

Study Population

This study was conducted in 2016 after the approval of Istanbul University Animal Experiments Local Ethics Committee dated 16.12.2016 and numbered 2016/78, following the conditions proposed by the Helsinki Declaration and Council of Europe decisions (ETS 123; 86/609/EEC). A total of 56 Sprague-Dawley male rats (16-20 weeks, weighing ranging from 300 and 350 grams) were used. During the experiment, animals were kept under standard laboratory conditions: free access to pellet feeds and water, accommodation in a temperature-controlled room (22-25°C), and a light-dark cycle of 12:12 hours were provided.

Table 1. Group Distributions

Group 1	n=7 male	Control
Group 2	n=7 male	Control 6th hour
Group 3	n=7 male	6th hour after spinal injury
Group 4	n=7 male	6th hour after spinal injury + 30 mg/kg methylprednisolone
Group 5	n=7 male	12th hour after spinal injury
Group 6	n=7 male	12th hour after spinal injury + 30 mg/kg methylprednisolone
Group 7	n=7 male	24th hour after spinal injury
Group 8	n=7 male	24th hour after spinal injury + 30 mg/kg methylprednisolone

Surgery

The surgical part of this study was carried out in the T.C. Istanbul University Prof.Dr. Aziz Sancar the Experimental Medicine Research Institute of Experimental Animal Research and Production Laboratory. Laminectomy was performed on Group 1 between T5-8 without clipping and T5-8 spinal cord tissue was excised. Laminectomy was performed on Group 2, but the spinal cord was excised at the 6th hour of laminectomy as described previously. The remaining 6 groups were clipped with the transient standard Yasargil aneurysm clip (FE 750) at 90 g pressure horizontally extradurally clamped to the dura and spinal cord circumferentially from the T5 level for 60 seconds. Spinal cord injuries were created to ensure trauma standards. After hemostasis, the layers were closed with 3/0 prolene according to anatomy. 30 mg/kg methylprednisolone (Mustafa Nevzat Drug, Istanbul) was administered intraperitoneally after clipping in groups 4-6-8,. The same procedures were performed on groups 3 and 4 at the 6th hour after clipping. Similarly, it was performed on groups 5 and 6 at the 12th hour and groups 7 and 8 at the 24th after clipping. T5-8 spinal cord tissue was excised without any damage (Table 1).

Histopathological Examination

The pathological examination and pictures of the produced preparations were performed in the T.C. Ministry of Health Beyoglu Public Hospitals Association Istanbul Okmeydani Training and Research Hospital Pathology Clinic. Spinal cord samples of all groups were placed in 10% formaldehyde solution and evaluated by a pathology specialist, who was employed in the Pathology Clinic of Okmeydanı Training and Research Hospital, who was unaware of the treatment groups, the treatments applied and the neurological evaluation results. After fixation, the samples were embedded in paraffin blocks and 5µm thick serial slicess were taken with a microtome and stained with Hematoxylin-Eosin (H-E). The preparations were examined histologically and morphologically with a light microscope (Zeiss, Oberkochem, Germany) at x40, x100, x200, and x400 magnifications.

Immunohistochemical Examination

Immunohistochemical staining was performed in Istanbul Sisli Tuzlali Pathology & Cytology Laboratory. TNF-α, IL-1, and IL-1β Antibodies were used for immunohistochemical examination. An immunohistochemical fixation protocol was applied (31). After the sections on the glass slides were deparaffinized, they were heated in the Citrate Buffer (pH:6) solution for proteolysis, at 700 Watts, in a microwave oven for 3X 5 minutes. Tissues were then incubated in a 3% H2O2 solution to prevent endogenous peroxidase activity. Following washing with 1Xphosphate buffer solution (PBS), the sections were incubated with serum for 60 min to prevent non-specific protein binding. was treated. Then, 1:300 diluted TNF-α, IL-1, and IL-1β were dripped onto the sections and kept at +4°C for overnight. Biotinylated secondary antibody was dripped onto the sections and incubated for 15 min at room temperature. It was kept for 15 minutes at room temperature in the streptavidin-HRP complex after washing and incubation. In the last step, 3,3'-diaminobenzidine (DAP) was used as the chromogen.

miRNA Isolation

The spinal tissues (~4 cm long and 0.5 cm thick), which were acquired via laminectomy in the lab employing experimental animals, were transferred by ice block to the lab where the analyses would be done (Anotolia Geneworks (Anatolia Diagnosis and Biotechnology Products R&D Industry and Trade Co. Kadikoy/Istanbul, Turkey)) within the first two hours. MicroRNA isolation from Serum, tissue and paraffin embedded tissue samples were performed by using Magrev microRNA Extraction Kit'. By following the company's instructions e ' First of all, Tissue miRNA Homogenization Buffer was added to the tissue samples and pretreated by pipetting. After pipetting, the tissue was incubated at 56 ºC for 45-80 minutes, during the incubation, the tubes were placed back in the heater by vortexing every 10 minutes.

Add 800 µl of MiR-Buffer 1 and 20 µl of Proteinase K to the LB tubes. Tissue sample treated with 400 µl buffer was transferred to each tube and mixed with a pipette. The magnetic block was placed on the stand and waited for 2 minutes. After the liquid in the tube was pipetted away, the magnetic block was removed, and the magnetic beads were suspended with 1000 µl of MiR-Buffer 2. This mixture was transferred to 1.5 ml microcentrifuge tubes located under the Magrev stand, and the magnetic slide at the bottom was pulled forward and waited for 1 minute. The liquid in the tube was carefully removed and 1000 µl of MiR-Buffer 3 was added while the magnetic slide was pulled. After it became homogeneous with a pipette, the inside of the tubes were washed and then MiR-Buffer 3 was removed. For DNAse 1 application, the

magnetic block was removed at this stage and the beads were suspended with 100 µl of DNAse 1. To prepare the DNAse 1 mix, 5 U of DNAse 1, DNAse Reaction Buffer 1 X and dH2O were made up to 100 µl in total volume. The mixture was incubated for 10 minutes at 37 °C.

After the tubes were removed from the heater block, 200 µl of MiR-Buffer 1 was added, and they were left at room temperature for 5 minutes. The samples were taken to the unit at the bottom, and after the sled was pulled forward, they were waited for 1 minute and the liquid in the tube was removed. Afterwards, the magnetic beads were suspended by adding 500 µl of MiR-Buffer 2 and the sled was pulled forward and waited for 1 minute. The liquid in the tube was removed and suspended by adding 500 µl of MiR-Buffer 4, the slide was pulled forward for 1 minute and the liquid was removed. MiR-Buffer 4 application was applied once again in the same way. While the magnetic slide was pulled, 1000 µl of MiR-Buffer 3 was added to the magnetic beads and the inside of the tubes were washed with this buffer, and then the buffer was removed. Afterwards, the tubes were treated with MiR-Buffer 6 with a volume of 500 µl, and the liquid was removed 1 minute after the sled was pulled. After the magnetic slide was pushed into place, 60 µl of MiR-Buffer 5 was added to the tubes and the tubes were incubated at 95 ºC for 10 minutes. After incubation, the tubes were placed in the lower unit and the sled was pulled forward and waited for 1 minute. The resulting elution was transferred to a clean tube and stored at -20 ºC for long-term storage.

Insulation Efficiency Analysis

Spectrophotometric Analysis

Spectrophotometric measurements of isolated miRNAs were performed by taking 1 µl from each sample (NanoPhotometer P 300, IMPLEN). Elution buffer (Buffer-5), which was used during Total RNA isolation, was used as the 'Blank'. The purity values of the RNAs isolated from the serum were 47.80 -118.00 ng/µl and their concentrations were determined. A 260/280 ratios were read between 1.84-2.01. Each RNA sample was diluted to 200 ng/µl to enter the PCR according to its concentration (Table 2).

Real Time PCR Analysis

rno-miR-24-3p and 2 different miRNAs (rno-miR-17-5p and rno-miR-30a-5p) were studied for normalization for a control 7 groups. The reaction was studied in 200 µl thin-walled PCR tubes with a 50 µl volume of Montania 4896 Real Time PCR Device.

Table 2. miRNA Primers (58)

miRNA Primers		
Primers	**(5‘-3‘)**	**Target Gene**
Primer 1-F	TGTAAACATCCTCGACTGGAAG	rno-miR-30a-5p
Primer 2-F	GGCAAAGTGCTTACAGTGC	rno-miR-17-5p
Primer 3-F	GTTTGGCTCAGTTCAGCAG	rno-miR-24-3p
Primer 4-R	GTGCAGGGTCCGAGGT	Universal R
Primer 5-F	GGGTGTAAACATCCTCGAC	rno-miR-30a-5p (not worked)
Primer 6-F	TGTGTTGTGTAAACATCCTCGAC	rno-miR-30a-5p (low yield)

PerfeCTa Universal PCR Primer (Quanta Biosciences) was used with miRNA forward primers. In addition, 2 different forward primers were used for miRNA 30a-5p, but

amplification data could not be obtained from 5-F, and amplification results with low efficiency (at high Ct) were obtained from 6-F.

In addition, a second Dnase 1 (Quanta Biosciences) application was performed to remove genomic DNA from the isolates. For this purpose, 1 µl of 10 x Reaction Buffer and 2 µl of PerfeCTa Dnase 1 for 7 µl of RNA were mixed by vortexing. After the mixture was incubated at 37 ºC for 30 minutes in PCR tubes, 1 µl of Stop Buffer was added and Dnase 1 activity was inactivated at 65º C for 10 minutes.

MiR-17, miR-24 and miR-30a were screened and their use as biomarkers were analyzed in the isolated control and experimental groups. In this context, qScript microRNA cDNA Synthesis Kit (Quanta Biosciences) was used to convert miRNAs to cDNA.

First of all, for the poly A tail addition reaction a mix is created and poly A tail synthesis incubations are performed at 37º C for 60 minutes and at 70º C for 5 minutes (Table 3).

Table 3. Poly A Tail Addition Reaction

Reaction Components	Concentration	Used Volume (µl)
Poly (A) Tailing Buffer	5X	2
Poly (A) Polymerase		1
Total RNA	100ng- 1 ug	7
	Total Volume	10 µl

For cDNA synthesis a mixture is created and incubated at 42 ºC for 20 minutes and at 85ºC for 5 minutes. PerfeCTa SYBR Green SuperMix (Quanta Biosciences) was used as a mix for Real Time PCR amplification of miRNAs translated into cDNA (Table 4).

Table 4. cDNA Synthesis

Reaction Components	Concentration	Used Volume (µl)
Poly A Reaction		10
MicroRNA cDNA Reaction Mix		9
qScript Reverse Transkriptase		1
	Total Volume	20 µl

For the amplification of miRNAs with Real Time PCR, a final volume of 50 µl is created in total and the amplification is performed with the following thermal protocol (Table 5) (Table 6).

Table 5. Amplifications With Real Time PCR

Reaction Components	Concentration	Used Volume (µl)
PerfeCTa SYBR Green SuperMix	2X	25
PerfeCTa microRNA Assay Primer (miR-127 ve miR-21)	10 µM	1
PerfeCTa Universal PCR Primer	10 µM	1
MicroRNA cDNA	(1-10 ng total RNA)	23
	Total Volume	50 µl

Ct (cycle threshold) is the name given to the number of cycles (threshold cycle) in real time PCR experiments where the amount of fluorescent signal exceeds the minimum value (threshold value) required to be observed. Ct parameter; Indicates the number of cycles in

which the detected fluorescence threshold is exceeded. Increases in PCR are logarithmic, so the following points should be taken into account when calculating the fold difference.

Table 6. Thermal Protocol for Amplification

Taq Polimerase activation	**95 ºC**	**2 minute**	
PCR Cycle	95 ºC	5 seconds	40 Cycle
	60 ºC	15 seconds	
	70 ºC	15 seconds	
	(floresan veri toplama)		
Melting Curve Analyse	50 ºC -90 ºC		

The 2-ΔΔCT method has been widely used as a relative quantification strategy for quantitative real-time polymerase chain reaction (qPCR) data analysis (32).

Values in a thermal protocol; It represents bindings between 0 and 40, and values close to zero indicate higher values. Values close to forty indicate a lower value.

The difference between the values in the thermal protocol is converted into a mathematical expression with 2-ΔΔCT (-ΔΔCT = amount of change) (change value over 2), followed by the expression increased if the value is displaced towards zero, and decreased if it is displaced towards forty.

Statistical Analysis

SPSS Windows version 24.0 package program was used for statistical analysis and $P<0.05$ was accepted as statistically significant. The conformity of the data to the normal distribution was tested with the Shaphiro Wilk test. In the comparison of numerical data in more than 2 independent groups, one-way analysis of variance (ANOVA) and LSD multiple comparison tests were used for normally distributed features, and Kruskal Wallis test and All pairwise multiple comparison test were used for non-normally distributed features. As descriptive statistics, mean±standard deviation was given for numerical variables, and number and % values were given for categorical variables.

RESULTS

When real time PCR results are examined;

⇒ According to the ΔΔCt results, the miR-30a was upregulated.

⇒ miR-17 was down regulated (Figure 1)

As a result of the statistical analysis;

- According to Kruskall Wallis test results for both miR-30a and miR-17, statistical difference between the groups was determined.

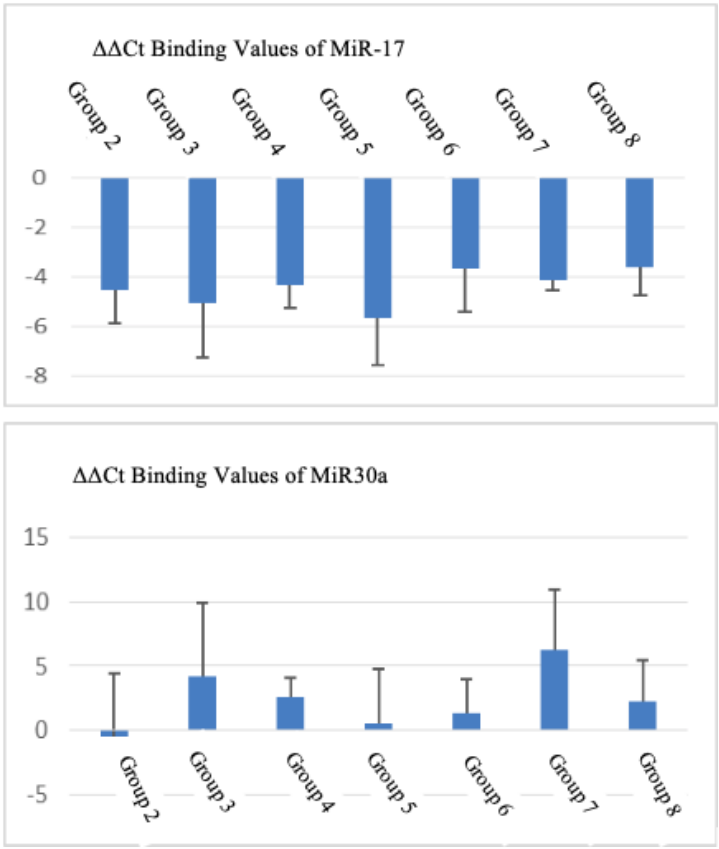

Figure 1. ΔΔCt Binding Values of MiR-17 and MiR30a.

All pairwise test was used for the difference between groups. According to the results of this test;

There was a significant difference of :

- miR-30a levels, between the 6th hour after laminectomy (Group 2) and the 24th hour after the damage (Group 7).
- miR-30a levels, between the 12th hour (Group 5) and the 24th hour (Group 7).
- miR-30a levels, between the 12th hour with methylprednisolone (Group 6) and the 24th hour without methylprednisolone (Group 7).
- miR-17 levels, between the 6th hour (Group 3) and the 24th hour with methylprednisolone (Group 8).
- miR-17 levels, between the 12th hour (Group 5) and the 12th hour with methylprednisolone (Group 6).
- miR-17 levels, between the 12th hour (Group 5) and the 24th hour (Group 7) .
- miR-17 levels, a between the 12th hour (Group 5) and the 24th hour with methylprednisolone (Group 8).

The gray matter-white matter transition was regular, the structures of neurons were in normal morphology and protected. No edematous tissues or necrosis was observed in the sections in the samples belonging to the control group (Figure 2).

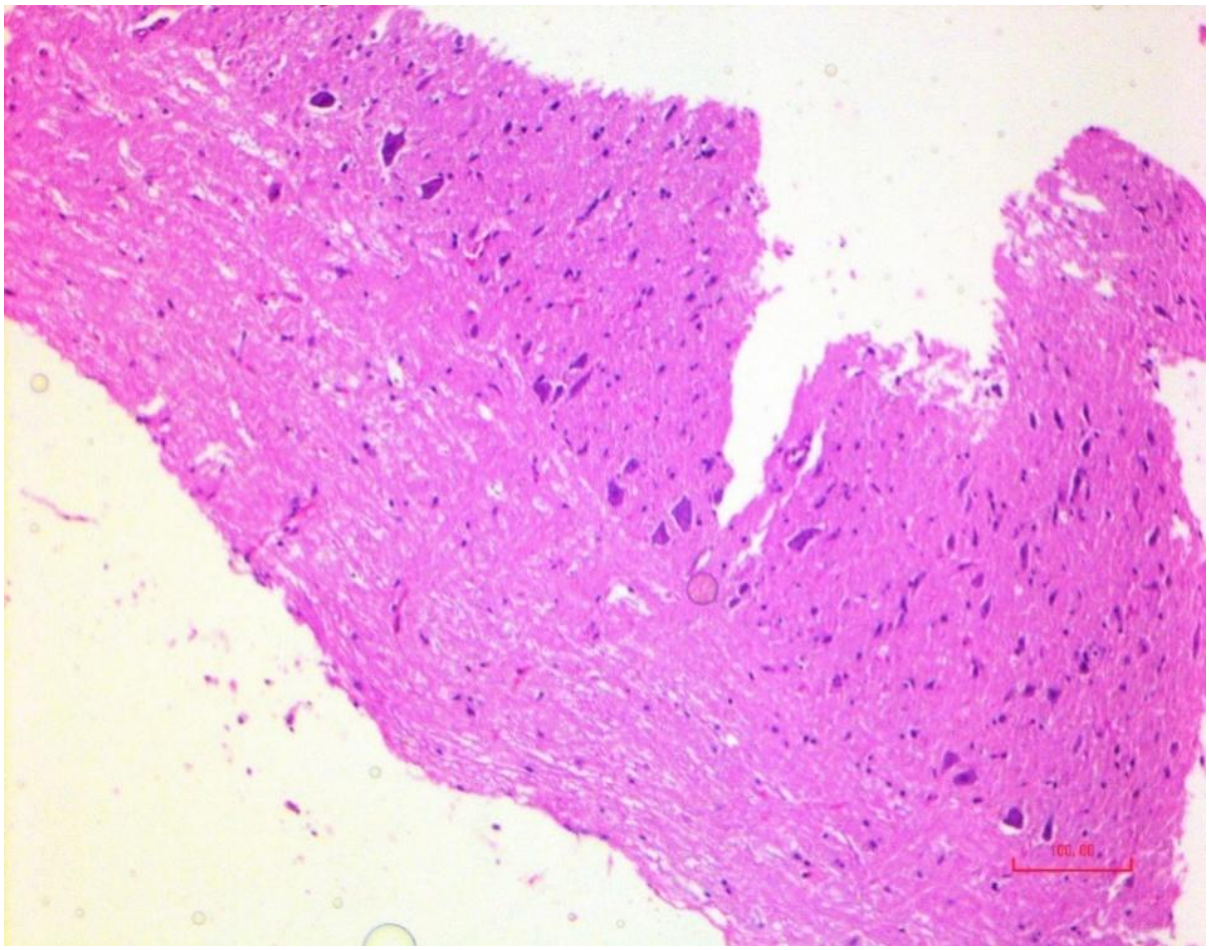

Figure 2. Examination of the control group with Haematoxylin-Eosin dye at x10 magnification. Gray matter-white matter transition is regular. Neurons in normal morphology.

The account of neurons decreased partially in the samples taken at the 6th hour (Group 3). Focal neuronal apoptosis was detected in some areas. The gray-white matter transition was regular. Mild focal edema were identified (Figure 3a). Focal light staining was observed in TNF-α, IL1, and IL1β staining. The account of neurons increased in the 6th-hour samples with methylprednisolone (Group 4) compared to the group without (Group 3). Apoptotic neurons and edema were decreased (Figure 3b). The cytoplasm dimension was decreased compared to nucleus in the samples taken at the 12th hour after spinal damage. The gray-white matter transition was vanished. Widespread apoptosis, hemorrhagic areas and mild edema were observed (Figure 3c). The neurons in regular morphology were partially increased at the 12th hour with methylprednisolone (Group 6) compared to the 12th hour without (Group 5). The gray matter-white matter transition was slightly fainted (Figure 3d). Hemorrhage was not observed in samples taken 24 hour (Group 7). Nissl bodies were detected in the cytoplasm. A large number of apoptotic dense nuclei neurons was observed (Figure 3e). Normal-looking neurons were significantly increased at the 24th hour with methylprednisolone (Group 8). Nissl bodies were decreased compared to those without methylprednisolone (Group 7). The gray matter-white matter transition became evident (Figure 3f).

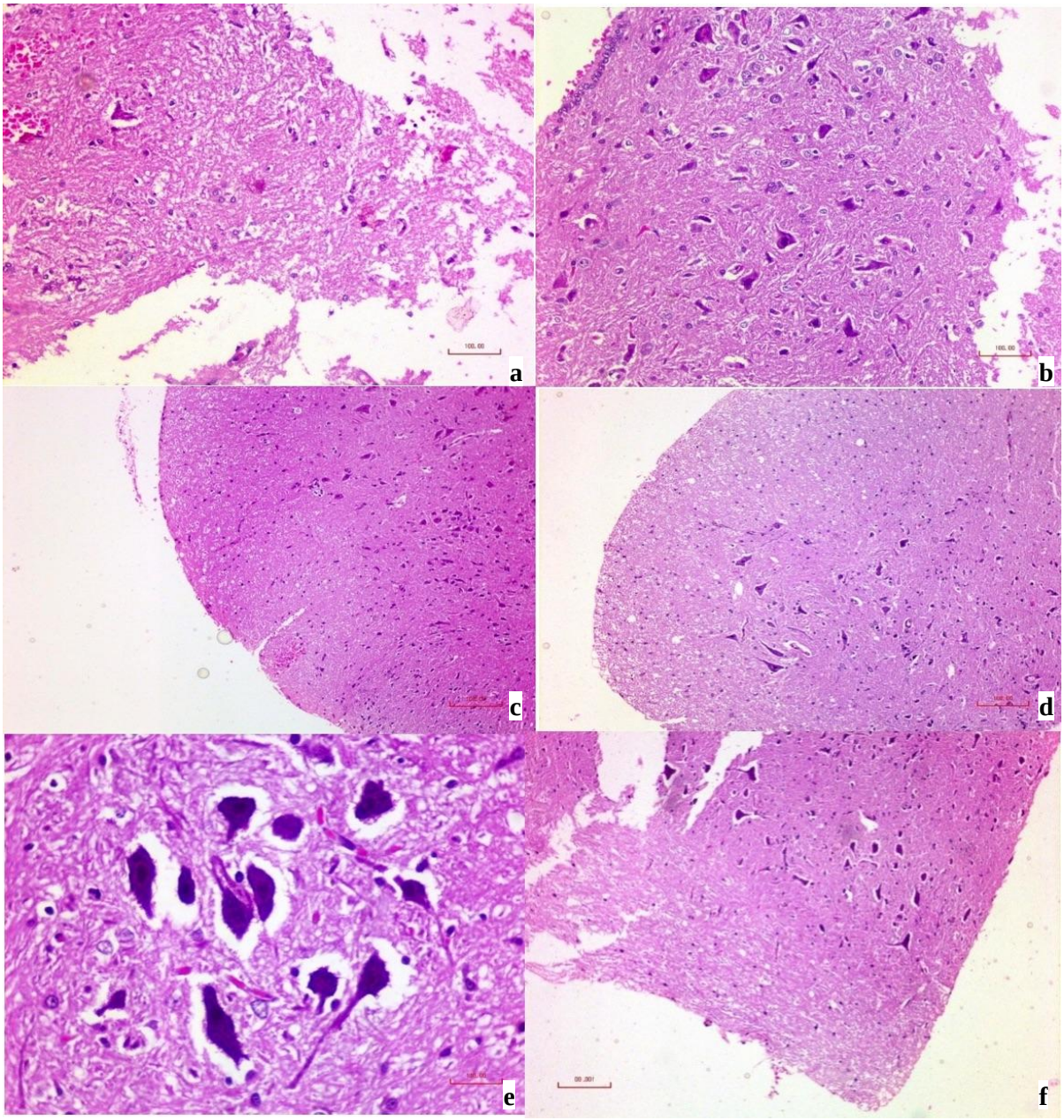

Figure 3. a) Image of the tissue at x20 magnification with Hematoxylin-Eosin dye at 6th hour after spinal damage. It appears that the number of neurons is reduced and there is mild edema. b) Examination of the group given methylprednisolone at the 6th hour after spinal injury with Hematoxylin-Eosin dye by x20 magnification. It was observed that the number of neurons increased compared to the group with spinal damage. c) Investigation of the group at the 12th hour after spinal injury with Hematoxylin-Eosin dye at x10 magnification. Significant reduction in gray-white matter transition was observed. d) Examination of the group given methylprednisolone at the 12th hour after spinal injury with Hematoxylin-Eosin dye by x10 magnification. It was observed that neurons in regular morphology increased. e) Examination of the group at the 24th hour after spinal injury with Hematoxylin-Eosin dye by x40 magnification. Nissl bodies showing. f) Examination of the group given methylprednisolone at the 24th hour after spinal injury with Hematoxylin-Eosin dye by x10 magnification. It was observed that the transition of gray-white matter became evident.

DISCUSSION

The majority of those exposed to spinal cord injuries are young active adults. For this reason, it is of great importance to investigate the methods of treatment both personally and communally and to conduct studies in this regard especially for the morbidity of the patients.

In addition to surgical and physical therapy combinations, pharmacological research continues throughout the world for spinal injuries. In these studies, it is mainly aimed, to prevent apoptosis by reducing the secondary effect of spinal cord injury, to increase axon regeneration, to prevent neuronal tissue replacement, scar and gliosis formation.

The effects of steroids have been emphasized especially in spinal cord injuries in the last century. For this purpose, many effects of steroids on the spinal cord have been investigated. Steroids have been shown to specifically prevent potassium loss from damaged cord tissue and facilitate extracellular calcium reuptake (33). The most beneficial effects of steroids in spinal cord injury are their inhibitory effects on lipid peroxidation and the maintenance of metabolic functions. It is also effective in reducing posttraumatic ischemia and slowing traumatic ion exchange (34).

Due to the widespread use of methylprednisolone in spinal cord injury, the NASCIS III study was initiated to investigate the effect of TrilazadmesylateTM treatment, which acts with the same mechanism due to its side effects. According to the results of this study, it was found that there was no difference between the patients when Trilazadmesylate and methylprednisolone were given in the first 3 hours, and methylprednisolone treatment has been found to be more effective in correcting motor functions between 3-8 hours (35).

Currently, although the effect and side effect profile of methylprednisolone is discussed, it has been proven to be effective on the lipid peroxidation mechanism. As a result of recent studies of human genes and functions, it has been revealed that the genome transcribes thousands of regulatory "non-coding" RNA (ncRNA) involved in live metabolism and reactions. These include micro RNA (miRNA), small interfering RNA (siRNA), P-element-induced Wimply Test (PIWI), interacting RNAs (piRNA), and various "long non-coding RNA" (ncRNA) (36).

miRNA biogenesis begins with the processing of RNA polymerase II-RNA polymerase III transcripts post or co transcriptionally (37). Approximately half of all now defined miRNAs are intragenic and processed usually from introns and comparatively few exons of protein coding genes, while the remaining are intergenic, transcribed independently of a host gene and arranged by their its promoters (38,39). Occasionally miRNAs are transcribed as one lengthy transcript named clusters, which may have similar seed regions, and in this status they are considered a family (40). The biogenesis of miRNA is categorized into canonical and non-canonical pathways (41).

Most researches until today have been showed that miRNAs bind to a specific sequence at the 3′-UTR of their target mRNAs to induce translational repression and mRNA deacetylation and decapping (42, 43). miRNA binding places have also been detected in other mRNA regions including the 5′-UTR and coding sequence, as well as within promoter regions (43). The linking of miRNAs to 5′-UTR and coding regions have silencing effects on gene expression while miRNA interaction with promoter region has been declared to induce transcription (44, 45). On the other hand, more studies are required to fully understand the functional importance of this kind of interplay (41).

Studies have been conducted on the relationship of microRNAs to many neuronal diseases and neurodegeneration, and the examination of the changes in spinal cord injury have been recently (46, 47). MiRNA values changed after spinal cord injury in rats were started to have been investigated by microarray analysis and real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) method. Previous studies have been shown increases in miRNA in spinal cord tissue (48).

Afterwards, was detected 269 of 350 miRNAs that were studied as a result of microarray analysis in the spinal cord of adult rats by Liu et al. These miRNAs were divided into four groups according to signal changes, those with low level (intensity <500), medium level (500–4999), high level (5000–9999) and highest level (>1000). In this study, significant changes was observed in 60 of 269 miRNAs detected after spinal cord injury. Changes in MiRNAs appeared at different times as down and up-regulation. Among these, it was observed that the miR-17 we selected in our study was down-regulated in the first 4 hours after spinal cord injury and showed marked upregulation on the 1st and 7th days. They also mentioned that miR17 along with miR-21, miR-145, miR-214, miR-133a, miR-133b, miR-674-5p, miR-15b, miR-20a, miR206, miR-672, miR-103 and miR-107, is a potential target for anti-apoptotic gene Bcl2-1 and Bcl2-2 after spinal cord injury of these miRNAs (49).

In another study under the action of intercellular adhesion molecule 1 (ICAM1), Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α) miR-181a, miR-411, miR-99a, miR-34a MiRNAs such as miR-30c, miR-384-5p and miR-30b-5p, miR-486 have been found to be downregulated, while miR-17, miR-20 and miR-124a are upregulated (50-53).

MiR-17 has been shown to take part in the inflammatory process that results in spinal cord injury. Upon the start of the inflammatory process, of miR-17 was held responsible for upregulation on the 1th day. In our study, the first 24-hour early spinal injury period was studied. As a result of our study, it was observed that miRNA-17-5p, which is a member of the miR-17 family, is the most downregulated in the 12th hour and this downregulation decreases significantly in the 24th hour. It was found that this downregulation, which occurred at the 12th hour, was significantly reduced with methylprednisolone. As a result of these results, it was determined that miR-17-5p was downregulated in the first 24 hours to peak at the 12th hour of spinal cord damage and that miR-17 down-regulation decreased at the 12th hour by administration of methylprednisolone. It was previously known that MiR-17-5p was upregulated after at the 24th hour for proliferation of cells such as astrocytes and oligodendrocytes in spinal cord injury. In our study, it is thought that miR-17-5p, which was detected to be down-regulated at the 12th hour, may also play a role in decreasing cell proliferation at the 24th hour. It was also stated in another study that miR-17 is specific for oligodendrocytes and increases the increase of oligodendrocyte proliferation cells by inhibition of the AKT pathway (54).

In a study by Chang et al., miR-30a was shown to be down-regulated. In our study, we determined that the spinal cord injury of miR-30a-5p was upregulated in the first 24 hours, which is the early damage period (55). It was observed that miR-30a-5p has the highest upregulation at the 6th hour after spinal injury, then this increase decreases and at the end of the 24th hour, the upregulation was at the lowest level. It was understood that the methylprednisolone is not effective at the 12th hour, by looking at the values of the 12th hour of the group with and without methylprednisolone. However, at the end of 24th hour, methylprednisolone was detected a decrease in miR-30a-5p upregulation. As can be seen from this, it is thought that methylprednisolone reduces miR-30a upregulation by affecting damage mechanisms occurring at the 24th hour.

Important steps have been taken with genetic studies on the mechanism of spinal cord injury. MicroRNAs has been shown to play an effective role in damage mechanisms, and methylprednisolone has been shown to be effective in providing treatment by affecting these microRNAs (56, 57). In the early injury period after spinal cord trauma, miRNAs previously detected in the spinal cord were shown to be up-regulated and down-regulated. Changes in this microRNA have been shown to vary with methylprednisolone, which is used in spinal cord injury.

CONCLUSION

In this study, it was observed that miR-17-5p was down-regulated and miR30a-5p was up-regulated after spinal cord injury in male Sprague-Dawley rats. In addition, the effect of methylprednisolone, which has been proven to have an effect on spinal cord damage but is controversial due to its side-effect profile, was investigated. It has been determined that miR-17-5p is effective in the down-regulation at the 12th hour after spinal cord injury with the effect of methylprednisolone. It was determined that the up-regulation of MiR-30a-5p was significantly reduced at the 24th hour by the effect of methylprednisolone.

It has been shown that miRNAs previously detected in the spinal cord are up-regulated and down-regulated in the early injury period after spinal cord trauma. It has been shown that changes in this microRNA change with methylprednisolone, which is used in spinal cord injury. Considering the side-effect profile of methylprednisolone, this study will lead to the development of new treatment methods over these microRNAs in the coming years, by revealing the mechanisms of microRNAs that can act on the spinal cord.

This study will lead to the development of new treatment methods over these microRNAs in the coming years by revealing the mechanisms of microRNAs that may have an effect on the spinal cord, considering the side effect profile of methylprednisolone.

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Covid-19 Enfeksiyon Öyküsü Olan ve Henüz Renal Replasman Tedavisi Almayan Kronik Böbrek Yetmezliği Hastalarında, Prediyaliz Hasta Eğitiminin Covid-19 Hastalık Seyri ve Renal Fonksiyonlar Üzerine Olan Etkisinin Araştırılması

Investigation of the Effect of Predialysis Patient Education on Covid-19 Disease Course and Renal Functions in Chronic Kidney Disease Patients with a History of Covid-19 Infection and Not Yet Receiving Renal Replacement Therapy

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Özet

Amaç: Kronik böbrek yetmezliği (KBY) olup Covid 19 enfeksiyonu geçiren olgularda prediyaliz hasta eğitiminin enfeksiyon sürecine ve renal fonksiyonların seyrine olan etkisinin incelenmesi.
Yöntem: Nefroloji Bilim Dalı'nda takipli olgular geriye dönük taranarak renal replasman tedavisi almayan KBY tanılı ve Covid-19 Hastalık öyküsü olan 98 hasta dahil edildi. Eğitim alan ve almayan grubun sigara, alkol, kullandığı ilaç, ek hastalık özellikleri, laboratuvar değerleri, favipiravir kullanımı, hastanede yatış öyküsü, entübasyon oranı, morbidite, mortalite oranı, seyirde hemodiyaliz ihtiyacı bakımından karşılaştırması yapıldı.
Bulgular: Vakaların %34,7'si eğitim almayan, %65,3'i eğitimli olarak saptandı. Eğitim almayan vakaların %38'inin, eğitimli vakaların ise %62,5'inin kadın olduğu bulundu. Eğitim almayan vakaların sigara kullanım oranı daha yüksek (p=0,008) bulundu. Eğitimli vakaların Covid-19 sonrası kreatinin değerinin Covid-19 öncesi kreatinin değerine göre azaldığı (p=0,004), GFR medyan değerlerinin anlamlı seviyede arttığı (p<0,001) bulundu. Eğitimli vakaların favipiravir kullanımının daha fazla olduğu (p=0,026) bulundu.
Sonuç: Çalışmamızda prediyaliz KBY hasta eğitiminin Covid-19 sonrası gelişebilecek renal fonksiyon kaybına sebep olmadığını hatta böbrek fonksiyonlarında iyileşme sağladığı gösterildi.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, Kronik Böbrek Yetmezliği, Hastaların Eğitimi.

Abstract

Objective: Investigation of the effect of predialysis patient education on the infection process and the course of renal functions in patients with chronic kidney failure (CKD) and Covid 19 infection.
Method: The cases followed in the Department of Nephrology were retrospectively scanned, and 98 patients with a diagnosis of CRF and a history of Covid-19 disease who did not receive renal replacement therapy were included. A comparison was made between the groups who received and did not receive training in terms of smoking, alcohol, drug use, additional disease characteristics, laboratory values, favipiravir use, hospitalization history, intubation rate, morbidity, mortality rate, and need for hemodialysis in the course.
Results: 34.7% of the cases were uneducated and 65.3% were educated. It was found that 38% of the uneducated cases and 62.5% of the educated cases were women. The rate of smoking was found to be higher in

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cases who did not receive education (p=0.008). It was found that the creatinine value of educated cases after Covid-19 decreased compared to the creatinine value before Covid-19 (p=0.004), and GFR median values increased significantly (p<0.001). It was found that educated cases had more favipiravir use (p=0.026).
Conclusion: In our study, it was shown that predialysis CKD patient education did not cause loss of renal function that may develop after Covid-19, and even improved kidney functions.

Key words: COVID-19, SARS-CoV-2, Chronic kidney failure, Education of patients.

GİRİŞ

2019 Aralık ayında Çin'den ortaya çıkan SARS-CoV-2'nin neden olduğu Covid-19 pandemisi, tüm dünyada küresel sağlık üzerinde önemli etkilere sebep olmuştur (1,2) Çoğu durumda semptomlar hafif olsa da, virüs akciğer ile birlikte kalp, sinir sistemi, böbrek gibi organları hasarlama kapasitesine sahip olabilir (3,4) Kronik böbrek yetmezliği (KBY); önceki yıllardaki grip gibi salgınlarda, genel popülasyonla karşılaştırıldığında artan mortalite ile ilişkili bir komorbiditedir (5). KBY hastaları daha yaşlı bireylerden oluşur; bu nedenle bu hastalarda ek hastalıklar ve belirli derecede immün disfonksiyon mevcuttur (5-7) KBY hastalarında pnömoni ve sepsis nedenli hastaneye yatış oranı daha yüksek ve hastanede yatış süresi daha uzun bulunmuştur (8). Ayrıca enfeksiyon, son dönem böbrek yetmezliği hastalarının ölüm nedenlerinin en başında gelir (9,10).

Kronik böbrek yetmezliği olup renal replasman tedavisi başlanmamış hastalarda prediyaliz hasta eğitiminin hastalık surveyi üzerine olumlu etkileri olmaktadır. Literatürde yer alan bir çok çalışmada prediyaliz hasta eğitimi alan olgularda diyalize gidiş sürecinin uzadığı, komplikasyon sıklığının azaldığı ve medikal tedaviuyumunun arttığı izlenmektedir (11-16). Yanı sıra uzun dönem eğitim alan hastalarda renal replasman tedavisi başlangıcında diyaliz sekansının belirlenmesi ve düzenlenmesinin de eğitim almayan hastalara nazaran daha anlaşılır ve kolay olduğu bu nedenle renal replasman tedavisi süresince de daha az komplikasyonla karşılaşıldığı bilinmektedir (17).

Covid-19 enfeksiyonu çeşitli immün mekanizmalar sonucunda birçok organda hasara yol açar. Akciğer lezyonlarının histopatolojik incelemesinde ödem, protein kaçışı, akciğer hücrelerinde fokal reaktif hiperplazi, enflamatuar hücresel komponentler tarafından lokal infiltrasyon izlenmiştir. Diğer tip ARDS'lere göre ciddi fibroz ile seyreden anormal iyileşme görülür (18,19).

Doku faktörü salınımı, fibrinojen artışı, endotelden Von Willebrant Faktör salınımı, akut enflamasyon nedeniyle antitrombin tüketimi, virüsün indüklediği endotel disfonksiyonu, kompleman aktivasyonu gibi olaylar nedeniyle koagülopati gelişir ve farklı organlarda tromboz karşımıza çıkar (20,21).

Kalp, Covid-19'da en fazla etkilenen organlardandır. Kalpteki ciddi enflamasyonun kalp kasına verdiği hasar, sitokin düzeylerindeki artışın miyokard hücrelerinde nekroza sebep olması nedeniyle Covid-19 hastalarında miyokardit, ritim bozukluğu ve miyokard enfarktüsü daha fazla görülmektedir (22).

Önceki koronavirüs enfeksiyonlarındaki gibi Covid-19 enfeksiyonu da karaciğeri tutmaktadır. Hastalar karaciğer fonksiyon testleri (KCFT) yüksekliği ile gelebilir veya hastalık seyrinde yükselebilir (23). Gastrointestinal sistemde ACE-2 reseptörleri bulunması nedeniyle Covid-19 hastaları bulantı, kusma, ishal, karın ağrısı gibi şikayetlerle başvurabilirler (24).

Covid-19 hastalığına yakalanan kişilerde akut böbrek hasarı geliştiği görülmüş, KBY olan kişilerin de böbrek fonksiyonlarının daha da azaldığı yapılan çalışmalarda gösterilmiştir. Hastalık seyrinde gelişen böbrek hasarının sebebi hemodinamik değişiklikler mi, yoksa virüsün doğrudan yaptığı direk hasar mı olduğu net değildir. Bu konu ile ilgili çeşitli araştırmalar mevcuttur. Bazılarında akut tübüler nekroz bulguları, bazılarında lenfosit infiltrasyonu, bazılarında kompleman birikimi, bazılarında podositlerde ve proksimal tübüller üzerinde virüsün direk sitopatik etkisinin bulguları saptanmıştır (25-27).

KBY' de Hasta Eğitiminin Klinik Etkileri

KBY gibi kronik hastalıkları olan hastalar için hasta eğitimi, başarılı sağlık davranışı değişiklikleri geliştirmek için kritik öneme sahiptir. Hastalara nefrologları, hemşireleri ve eğitim ekibi tarafından diyaliz öncesi eğitim verilmesi ve hastaların düzenli eğitim programlarına katılması böbrek hastalıklarının ilerlemesini ve böbrek yetmezliği sonucu gelişebilen istenmeyen durumları ve yan etkileri (kansızlık, hipertansiyon, beslenme bozuklukları, kemik hastalıkları, kan asit yükünün artması gibi durumlar) azaltabilmektedir. Bu hastaların sakatlık ve ölüm oranları daha düşük olmaktadır. Yaşam kaliteleri artmakta, acil diyaliz gereksinimleri azalmaktadır. Yine bu eğitimlere katılan hastalarda daha çok planlı bir diyalize başlama, fistül veya kalıcı kateterle diyalize başlama veya diyalize hiç girmeden direkt böbrek nakline gidiş (pre-emptif) söz konusu olabilmektedir. Eğitim programlarına katılmayan veya eğitimlere geç yönlendirilen özellikle yaşlı hastalarda ise erken ölüm ve sakat kalma riski artmakta, hastane yatış süreleri daha uzun olmakta, maliyetler artmakta ve bu hastalarda daha çok geçici katater kullanımının olduğu, acil olarak diyalize alınma riskinin daha yüksek olduğu görülmektedir (28-36).

KBY'de Hasta Eğitiminin Bileşeni Olan Beslenme Alışkanlıkları ve Yaşam Tarzı Değişiklikleri

KBY ile ilgili birçok risk faktörü hasta eğitimi ile değiştirilebilir. Hipertansiyon, proteinüri, sigara, alkol alımı, hareketsizlik, düzensiz egzersiz, obezite, yeterince su tüketmeme, hiperglisemi, hiperfosfatemi, hiperürisemi, aşırı tuz tüketimi, aşırı kırmızı et tüketimi, doymuş ve trans yağ asitlerinin yüksek tüketimi, nefrotoksik ilaç kullanımı (NSAID'ler, iyotlu kontrast maddeler, aminoglikozit antibiyotikler, metformin, vb.) gibi KBY ilerlemesinde risk faktörü olan durumların çoğu, iyi hasta eğitimi ve bakımı ile azaltılabilir veya ortadan kaldırılabilir. Ayrıca hasta eğitimi, antihipertansif ilaç ihtiyacını azaltır, günlük alınan toplam ilaç sayısını azaltır ve kronik böbrek hastalarında sigara ve aşırı tuz alımını ve nefrotoksik ilaç kullanımını azaltmaya yardımcı olur (32-36).

Beslenme Alışkanlıkları ve Yaşam Tarzının İmmün Sistem Üzerine Etkisi

Beslenme, immün sistemin %85'ini oluşturur. Bağırsak mikrobiyotasının sağlığını geliştirmesini ve arttırmasını sağlar. Bulaşıcı olan ve olmayan çoğu hastalıktan korunmak iyi bir immün sisteme bağlıdır. Yeterli miktarda yeşil yapraklı sebze, lif bakımından zengin olan baklagil ve tahılların tüketimi immün sistemi güçlendirmektedir (37). Fiziksel aktivitenin diyabet, obezite gibi hastalıklara karşı koruyucu ve tedavi edici etkileri bilinmektedir. Fiziksel aktivite yürüyüş, bisiklete binme ve dans, yoga gibi birçok farklı sekilde gerçekleştirilebilir. Düzenli egzersiz ve spesifik beslenme stratejileri, immün sistemin güçlenmesi için başlıca stratejilerdir (38). Evde uzun süre zaman geçirmek; hareketsizliğin artmasına ve kalori harcamasındaki azalmayla birlikte kronik hastalıkların ortaya çıkması ve/veya ilerlemesi, kas gücü ve kitlesinde kayba neden olmaktadır. Ek olarak immün kayıp oluşturarak viral enfeksiyon riskini arttırmaktadır (39).

Doğru ve uygun beslenme kurallarını ve yaşam tarzı değişikliklerini öğrenmek, her aşamada KBY olan hastalar için hayati önem taşır. Hastalar, doğru yiyecek ve içecekleri tüketerek ve sodyum, potasyum ve fosfordan kaçınarak KBY 'ye bağlı bazı sağlık sorunlarını önleyebilir veya geciktirebilir (40). KBY' de üremi ile ilişkili olarak bağışıklık sisteminin işlevleri azalmıştır. Böbrek fonksiyonunun ilerleyici kaybı, lenfoid hücre soyu üzerinde, naif T ve B hücrelerinin sayısının azalmasına, T hücre farklılaşmasının artmasına ve telomer uzunluğunun kaybına neden olan derin bir etki ile ilişkilidir. Bu edinilmiş immün yetmezliğin morbidite ve mortalite üzerindeki sonuçları önemlidir, çünkü KBY hastalarının en sık ölüm sebebi enfeksiyonlardır (41).

Beslenme İmmün Sistem ile Covid-19 İlişkisi

Sağlıklı bir immün sistem yanıtı, yeterli ve dengeli beslenmeye bağlıdır. Örneğin, yeterli protein alımı, optimal antikor üretimini destekler. D vitamini, antikor salgılayan hücreleri aktive eder ve A vitamini, T hücre çoğalmasını uyarır. Vitaminler (A, B6, B12, C, D, E ve folat), eser elementleri (yani çinko, demir, selenyum, magnezyum ve bakır) ve omega-3 yağ asitleri (eikosapentaenoik asit (EPA) ve dokosaheksaenoik asit (DHA)), bağışıklık fonksiyonunu geliştirmek için tamamlayıcı bir rol oynamaktadır. Mikro besinler immünomodülasyon için hayati öneme sahiptir ve eksiklikleri viral enfeksiyonlara duyarlılığı artırabilir (42).

Yapılan çalışmalardan çıkan sonuçlar SARS-CoV2'nin yaşlı, komorbid ve hipoalbüminemik olgularda daha ciddi sorunlar oluşturduğunu göstermektedir. Ve bu çalışmalarda Covid-19'dan korunma ve tedavide beslenmenin oldukça önemli olduğu vurgulanmaktadır. Sarkopeni ve vücut kitle indeksinin yüksek olması Covid-19'lu vakalarda kötü prognoz ile ilişkili bulunmuştur. Ek olarak yetersiz beslenme de kötü prognoz kriterlerindendir (43). Bütün viral enfeksiyonlarda olduğu gibi Covid-19 da immün sistemi düşük olan kişilerde daha sık izlenmektedir (44). Protein ve kaloriden zayıf beslenme; hastalıklara karşı immün sistemi zayıflatmakta ve bulaşıcı hastalık riskini arttırmaktadır. Ayrıca yapılan bir çalışmada protein ve enerjiden yoksun beslenme sonucunda Influenza enfeksiyonuna yanıt olarak artan yaşla birlikte artan bir mortalite görülmüştür. Bu durumun sebebinin vücut kitle indeksinin düşük olması nedeniyle immün sistemin yeterli güce sahip olmaması olabilir (45).

Prediyaliz KBY Hastalarına Tarafımızca Verilen Hasta Eğitimin Özellikleri

Prediyaliz hasta eğitimi, günümüz modern tıbbı ile böbrek fonksiyonlarını iyileştirmenin yanı sıra hastaların sosyal ve psikolojik durumlarını iyileştirmeyi, immün sistemi daha güçlü hale getirerek enfeksiyonlardan korumayı, enfeksiyona yakalanma durumunda daha hafif atlatmayı amaçlamaktadır.

Daha önce tarafımızca yapılan çalışmalarda bu eğitimi uygulayan hastaların KBY' ye bağlı morbidite ve mortalitesinin azaldığı, yaşam kalitesinin arttığı gösterilmiştir (46). Tarafımızca verilen prediyaliz hasta eğitiminin bileşenleri; hasta ve bakıcı eğitimi, yaşam tarzı değişiklikleri, beslenme ve düzenli egzersiz, doğru dozlarda doğru ilaçların kullanımı, moral ve motivasyon desteği, sıvı dengesi ayarı, rezidü böbrek fonksiyonlarını koruma ve nefroprotektif alternatif tıp tedavileridir (Şekil 6) (47). Sosyal medya aracılığı ile hastaların diyet ve yaşam tarzı ile ilgili sorularını yanıtlamak için, eğitici videolar düzenleyerek hasta ve bakıcılarının eğitimi amaçlandı. Pandemi nedeniyle toplantılar düzenlenemedi. Poliklinik kontrolleri sırasında hastaların tuz alımı azaltılıp, yerine böbrek dostu baharatlar ve şifalı bitkiler koyuldu. Sigara kesilerek egzersiz süresi arttırıldı. Zararlı içecekler, işlenmiş etler, margarin ve beyaz unlu mamüller yasaklanarak böbrek dostu ürünlerle değiştirildi. Günlük protein alım miktarı azaltıldı. Güneş banyosu önerildi. Hem hastalarda hem hasta bakıcılarda

varolan depresyon ve anksiyete tedavi edildi. Siesta uygulaması başlatılarak hastalarımızdaki bozulmuş uyku paterni düzenlendi. Hastaların tüm takipleri aynı nefrolog tarafından yapıldı. Hastalarımız herhangi bir soru sormak istediklerinde 7 gün 24 saat nefrologları ile doğrudan iletişime geçecek şekilde haberleşmeleri sağlandı.

YÖNTEM

Çalışma Dizaynı ve Hastalar, İstatistiksel Analiz

Çalışmamızda Mart 2020 - Aralık 2021 tarihleri arasında Nefroloji Polikliniği'ne başvuran renal replasman tedavisi almayan KBY tanılı ve Covid-19 hastalık öyküsü (nazofaringeal sürüntü çubuğu ile PCR pozitif saptanan hastalar) olan98 hastadan elde edilen veriler retrospektif olarak incelendi.Bunlardan Covid- 19 hastalığı öncesi en az 1 yıl süre ile takibimizde olan hastalar, eğitimli grup olarak adlandırıldı. 1 yıldan daha az süre takip ettiğimiz hastalar, eğitimli olmayan grup olarak adlandırıldı. Seçilen hastaların demografik verileri (yaş, cinsiyet), laboratuvar bulguları (kan glukozu, tam kan sayımı, üre, kreatinin, sodyum, potasyum, kalsiyum, fosfor, Chronic Kidney Disease Epidemiology Collaboration' a göre glomeruler filtrasyon hızı), eğitimli hasta olup olmadığı, seyirde hemodiyaliz ihtiyacı, favipravir kullanımı, mortalite oranı, entübasyon öyküsü oranı, yoğun bakım ihtiyacı, hastanede yatıp yatmadığı, hastanede yattıysa yatış süresi, morbidite oranı (serebrovasküler olay (SVO), miyokard enfarktüsü (MI), pulmoner emboli vs.) dijital ortamda kayıt altına alınıp SPSS programına kaydedildi. Böylece istatiksel hesaplamalar yapılarak iki grubun karşılaştırılması yapıldı. Tüm analizler için anlamlılık seviyesi $p<0,05$ olarak belirlendi. Analizlerin uygulamasında IBM SPSS 22.0 programı kullanıldı.

Etik Onay

Araştırma, Helsinki Deklerasyonu'na uygun olarak yürütülmüş olup, çalışmanın gerçekleştirilebilmesi için Balıkesir Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan izin alınmıştır (Tarih: 26.05.2021/ Sayı: 2021/118).

BULGULAR

Araştırmada değerlendirilen 98 vakanın 34'ü (%34,7) eğitim almayan, 64ü (%65,3) eğitimliydi. Eğitim almayan vakaların 13'ünün (%38,2), eğitimli vakaların ise 40'ının (%62,5) kadın olduğu bulundu (Tablo 1).

Tablo 1. Araştırmada Değerlendirilen Eğitim Alan Ve Almayan Vakaların Yaş Ve Cinsiyet Özelliklerinin Karşılaştırılması

		EĞİTİM				
		Eğitimsiz (n=34)		Eğitimli (n=64)		
		n	%	n	%	p
CİNSİYET	**KADIN**	13	**38,2**	40	**62,5**	**0,022[a]**
	ERKEK	21	61,8	24	37,5	
		Ort.	SS.	Ort.	SS.	
YAŞ		57,77	18,04	60,03	14,00	0,493[b]

Eğitim almayan vakaların sigara kullanım oranlarının, eğitimli vakaların sigara oranlarından istatistiksel açıdan anlamlı seviyede daha yüksek olduğu (p=0,008) bulundu (Tablo 2).

Tablo 2. Araştırmada Değerlendirilen Eğitim Alan Ve Almayan Vakaların Sigara, Alkol Ve Kullandığı İlaç Özelliklerinin Karşılaştırılması

		EĞİTİM				
		Eğitimsiz		Eğitimi olan		
		n	%	n	%	P[a]
SİGARA	Hayır	27	79,4	62	96,9	**0,008***
	Evet	7	**20,6**	2	**3,1**	
ALKOL	Hayır	32	94,1	63	98,4	0,275*
	Evet	2	5,9	1	1,6	
OAD	Hayır	23	67,6	54	84,4	0,055
	Evet	11	32,4	10	15,6	
İNSÜLİN	Hayır	33	97,1	54	84,4	0,091*
	Evet	1	2,9	10	15,6	
ACEİ	Hayır	31	91,2	59	92,2	0,862
	Evet	3	8,8	5	7,8	
ARB	Hayır	28	82,4	58	90,6	0,234
	Evet	6	17,6	6	9,4	
CaKB	Hayır	21	61,8	34	53,1	0,412
	Evet	13	38,2	30	46,9	
BB	Hayır	19	55,9	28	43,8	0,252
	Evet	15	44,1	36	56,3	
DİÜ	Hayır	26	76,5	55	85,9	0,239
	Evet	8	23,5	9	14,1	
MG	Hayır	32	94,1	57	89,1	0,402
	Evet	2	5,9	7	10,9	
NAHCO3	Hayır	17	50,0	29	45,3	0,658
	Evet	17	50,0	35	54,7	
VİT D	Hayır	22	64,7	36	56,3	0,418
	Evet	12	35,3	28	43,8	

a=Ki-Kare Analizi, *Fisher's Exact Test Sonucu
OAD: Oral antidiabetik ilaç, ACEİ: Ace İnhibitörü, ARB: Aldosteron reseptör blokeri, CaKB: Kalsiyum kanal blokeri, BB: Beta bloker, DİÜ: Diüretik, MG: Magnezyum preparatı, NAHCO3: Sodyum bikarbonat, VİT D: Vitamin d preparatı.

Eğitim alan ve almayan vakalar arasında ek hastalık özellik oranlarının istatistiksel açıdan anlamlı seviyede farklı olmadığı bulundu (Tablo3).

Tablo 3. Araştırmada Değerlendirilen Eğitim Alan Ve Almayan Vakaların Ek Hastalık Özelliklerinin Karşılaştırılması

		EĞİTİM				
		Eğitimsiz		Eğitimi olan		
		n	%	n	%	P[a]
DM	Hayır	24	70,6	47	73,4	0,764
	Evet	10	29,4	17	26,6	
HT	Hayır	9	26,5	13	20,3	0,487
	Evet	25	73,5	51	79,7	
PKBH	Hayır	33	97,1	60	93,8	0,656*
	Evet	1	2,9	4	6,3	
NEFROLİTİAZİS	Hayır	33	97,1	61	95,3	0,999*
	Evet	1	2,9	3	4,7	
GLOMERULONEFRİT	Hayır	32	94,1	57	89,1	0,409
	Evet	2	5,9	7	10,9	
FMF	Hayır	33	97,1	64	100,0	0,347*
	Evet	1	2,9	0	0,0	
ASKH	Hayır	26	76,5	40	62,5	0,160
	Evet	8	23,5	24	37,5	

a=Ki-Kare Analizi, *Fisher'sExact Test Sonucu
DM: Diabetes Mellitus, HT: Hipertansiyon, PBKH: Polikistik Böbrek Hastalığı, FMF: Ailevi Akdeniz Ateşi, ASKH: Aterosklerotik koroner kalp hastalığı.

Eğitim alan ve almayan vakalar arasında Covid-19'a yakalanmadan önceki son 6 ay içinde glomeruler filtrasyon hızı (GFR) ve kreatinin değerleri ortalamalarının istatistiksel açıdan anlamlı derecede farklılık göstermediği bulundu (Tablo 4). Yani tüm hastalar Covid-19'a yakalanmadan önce böbrek fonksiyonları açısından aralarında fark yoktu.

Tablo 4. Araştırmada Değerlendirilen Eğitim Alan Ve Almayan Vakaların Covid-19 Öncesi Son 6 Aydaki GFR Ve Kreatinin Değerlerinin Karşılaştırılması

	EĞİTİM										
	,00					1,00					
	Ort.	SS.	Med.	%25	%75	Ort.	SS.	Med.	%25	%75	p
SON 6 AY GFR ORT	27,20	18,10	20,50	13,36	40,00	26,11	17,05	21,35	12,87	37,16	0,737b
SON 6 AY KR ORT.	3,23	1,96	3,23	1,59	3,87	3,15	1,76	2,84	1,71	4,06	0,941b

Eğitim almayan vakaların Covid-19 sonrası üre (p=0,040) ve kreatinin (p=0,008)medyan değerlerinin Covid-19 öncesi üre ve kreatinin medyan değerlerine göre istatistiksel açıdan anlamlı seviyede arttığı, GFR (p=0,014) medyan değerinin iseistatistiksel açıdan anlamlı seviyede azaldığı bulundu .Eğitim almayan vakaların Covid-19 sonrası fosfor medyan değerlerinin Covid-19 öncesi fosfor medyan değerlerine göre istatistiksel açıdan anlamlı seviyede arttığı (p=0,043) bulundu (Tablo 5).

Tablo 5. Araştırmada Değerlendirilen Eğitim Almayan Vakaların Covid-19 Sonrası Laboratuvar Değerlerinin Değişimi

		Ort.	SS.	Med.	%25	%75	p
GLUKOZ	Öncesi	113,29	45,80	98,50	91,00	116,00	0,087a
	Sonrası	99,45	20,20	94,00	86,00	110,00	
ÜRE	Öncesi	105,15	59,56	**101,00**	56,00	130,00	**0,040a**
	Sonrası	116,29	72,79	**105,50**	52,00	150,00	
KRE	Öncesi	4,06	3,12	**3,80**	2,16	4,85	**0,008a**
	Sonrası	4,43	2,47	**3,97**	2,80	4,68	
GFR	Öncesi	26,70	18,21	**20,24**	13,00	41,15	**0,014a**
	Sonrası	23,17	18,69	**14,55**	11,20	40,00	
PTH	Öncesi	182,30	150,41	160,00	71,00	260,00	0,863a
	Sonrası	175,08	139,85	156,00	70,00	221,50	
Na	Öncesi	137,88	3,85	139,00	135,00	141,00	0,320b
	Sonrası	138,52	2,63	139,00	137,00	140,00	
K	Öncesi	4,82	,61	4,80	4,50	5,10	0,626a
	Sonrası	4,88	,52	4,80	4,50	5,20	
Ca	Öncesi	9,02	,75	9,10	8,40	9,60	0,077b
	Sonrası	9,26	,71	9,30	8,60	9,80	
P	Öncesi	4,52	1,34	**4,25**	3,70	5,00	**0,043a**
	Sonrası	4,87	1,79	**4,90**	3,90	5,20	
Mg	Öncesi	2,18	,38	2,10	1,90	2,30	0,693a
	Sonrası	2,17	,29	2,10	1,90	2,30	
HGB	Öncesi	11,63	2,04	11,85	10,40	13,00	0,247b
	Sonrası	11,56	2,33	11,60	9,90	13,30	
ÜA	Öncesi	7,25	1,59	7,30	6,00	8,00	0,502b
	Sonrası	7,40	2,20	7,30	5,80	8,10	
CRP	Öncesi	6,64	6,47	3,00	3,00	7,20	0,487a
	Sonrası	9,26	12,31	3,00	3,00	12,40	
SPOT	Öncesi	2647,24	3408,62	1606,00	700,00	3120,00	0,538a
	Sonrası	2432,46	3411,92	1421,00	855,10	2429,00	

Ort.=Ortalama, SS.=Standart Sapma, a=Wilcoxon İşaretli Sıralar Testi, b=Bağımlı Gruplar t testi, Kre: Kreatin, GFR: Glomeruler Filtrasyon Hızı, PTH: Parathormon, Na: Sodyum, K: Potasyum, Ca: Kalsiyum, P: Fosfor, Mg: Magnezyum, WBC: Lökosit, HB: Hemoglobin, CRP: C-Reaktif Protein SPOT: Spot idrar protein/kreatin oranı.

Eğitimli vakaların Covid-19 sonrası kreatinin medyan değerlerinin Covid-19 öncesi kreatinin medyan değerlerine göre istatistiksel açıdan anlamlı seviyede azaldığı (p=0,004) bulundu (Tablo 6).

Eğitimli vakaların Covid-19 sonrası GFR medyan değerlerinin Covid-19 öncesi GFR medyan değerlerine göre istatistiksel açıdan anlamlı seviyede arttığı (p<0,001) bulundu (Tablo 6).

Eğitimli vakaların Covid-19 sonrası hemoglobin değer ortalamalarının Covid-19 öncesi hemoglobin değer ortalamalarına göre istatistiksel açıdan anlamlı seviyede azaldığı (p=0,002) bulundu (Tablo 6).

Tablo 6. Araştırmada Değerlendirilen Eğitimli Vakaların Covid-19 Sonrası Laboratuvar Değerlerinin Değişimi

		Ort.	SS.	Med.	%25	%75	p
GLUKOZ	Öncesi	117,36	48,87	98,50	90,00	119,00	0,917a
	Sonrası	116,81	55,01	95,00	87,00	117,00	
ÜRE	Öncesi	99,91	54,29	83,00	57,50	142,00	0,297b
	Sonrası	96,42	52,89	86,00	58,00	117,00	
KRE	Öncesi	3,36	1,73	**3,16**	1,76	4,49	**0,004a**
	Sonrası	3,39	2,47	**2,93**	1,80	4,07	
GFR	Öncesi	24,33	15,55	**19,85**	11,62	35,74	**<0,001a**
	Sonrası	25,29	17,73	**20,44**	12,65	33,36	
PTH	Öncesi	247,21	204,51	200,50	89,70	325,60	0,150a
	Sonrası	206,36	143,64	179,30	99,00	281,00	
Na	Öncesi	138,39	2,15	138,00	137,00	140,00	0,740b
	Sonrası	138,23	2,69	138,00	137,00	140,00	
K	Öncesi	4,87	,60	4,80	4,40	5,30	0,999b
	Sonrası	4,81	,61	4,70	4,40	5,30	
Ca	Öncesi	9,07	,81	9,20	8,75	9,60	0,960a
	Sonrası	9,12	,84	9,30	8,70	9,70	
P	Öncesi	4,38	1,26	4,10	3,55	5,05	0,240a
	Sonrası	4,40	1,19	4,20	3,60	5,10	
Mg	Öncesi	2,19	,31	2,20	2,00	2,30	0,852a
	Sonrası	2,19	,27	2,20	2,00	2,30	
HGB	Öncesi	12,12	2,04	**12,15**	10,70	13,45	**0,002b**
	Sonrası	11,56	2,33	**11,60**	9,90	13,30	
ÜA	Öncesi	7,25	1,59	7,30	6,00	8,00	0,869b
	Sonrası	7,40	2,20	7,30	5,80	8,10	
CRP	Öncesi	6,64	6,47	3,00	3,00	7,20	0,376a
	Sonrası	9,26	12,31	3,00	3,00	12,40	
SPOT	Öncesi	2647,24	3408,62	1606,00	700,00	3120,00	0,088a
	Sonrası	2432,46	3411,92	1421,00	855,10	2429,00	

Ort.=Ortalama, SS.=Standart Sapma, a=Wilcoxon İşaretli Sıralar Testi, b=Bağımlı Gruplar t testi, Kre: Kreatin, GFR: Glomeruler Filtrasyon Hızı, PTH: Parathormon, Na: Sodyum, K: Potasyum, Ca: Kalsiyum, P: Fosfor, Mg: Magnezyum, WBC: Lökosit, HB: Hemoglobin, CRP: C-Reaktif Protein SPOT: Spot idrar protein/kreatin oranı.

Eğitimli vakaların favipiravir kullanım oranlarının, eğitim almayan vakaların favipravir kullanım oranlarından istatistiksel açıdan anlamlı seviyede daha yüksek olduğu (p=0,026) bulundu. Buna ek olarakeğitim alan ve almayan vakalar arasında hastayaneye yatış, sonlanım noktası farklılığı, entübasyon oranı, seyirde SVO, MI gibi komplikasyon gelişimi, mortalite oranı, seyirde geçici HD ihtiyacı ve seyirde rutin HD ihtiyacıoranlarının istatistiksel açıdan anlamlı seviyede farklılık göstermediği bulundu (Tablo 7).

Tablo 7. Araştırmada Değerlendirilen Eğitim Alan Ve Almayan Vakaların Tedavi Ve Yatış Özelliklerinin Karşılaştırılması

		EĞİTİM				
		Eğitim almayan		Eğitim alan		
		n	%	n	%	p
FAVİPİRAVİR	Hayır	12	35,3	10	15,6	**0,026**
	Evet	22	**64,7**	54	**84,4**	
HASTANEYE YATIŞ	Hayır	21	61,8	31	48,4	0,208
	Evet	13	38,2	33	51,6	
SONLANIM NOKTASI (0 ev servis 1 ybü 2)	0	21	61,8	31	48,4	0,441
	1	8	23,5	19	29,7	
	2	5	14,7	14	21,9	
ENTÜBASYON	Hayır	30	88,2	53	82,8	0,478
	Evet	4	11,8	11	17,2	
MORBİDİTE (SVO,MI,..)	Hayır	31	91,2	58	90,6	0,928
	Evet	3	8,8	6	9,4	
MORTALİTE	Hayır	31	91,2	53	82,8	0,260
	Evet	3	8,8	11	17,2	
GEÇİCİ HD İHTİYACI	Hayır	24	70,6	49	76,6	0,518
	Evet	10	29,4	15	23,4	
SEYİRDE RUTİN HD	Hayır	28	82,4	60	93,8	0,076
	Evet	6	17,6	4	6,3	

TARTIŞMA

Yapmış olduğumuz bu çalışma ile renal replasman tedavisi almayan KBY hastalarında hasta eğitiminin Covid-19 enfeksiyonuna yakalanma durumunda böbrek fonksiyonlarında iyileşme sağladığı ancak hastaneye yatış, yatış süresi, entübasyon, hastalık seyrinde morbidite ve mortalite gelişimi, seyirde hemodiyaliz ihtiyacı ve hastalık sonrası rutin hemodiyaliz gereksinimi arasında ilişki olmadığı gösterilmiştir. Elde edilen diğer bulgular literatür ışığında tartışılmıştır. Çalışmamızda eğitimli grupta kadınların daha ön planda olduğunu gördük (%62.5 vs %38.2, p=0,022). Bu durum kadınların eğitime daha açık olduğunu ve ayrıca kadınlara eğitim verilmesi durumunda daha başarılı olunduğunu göstermektedir.Bizim çalışmamızda eğitimli hasta grubumuzda sigara içme oranı anlamlı olarak düşük çıkmıştır (%3vs%20.6, p=0.008). Bu durum eğitimin sigara üzerindeki etkisini göstermektedir. Çünkü eğitimli grup sigaranın kronik böbrek yetmezliğini kötüleştirdiği ile ilgili ve Covid-19'a yakalanma durumunda hastalığın kötü seyrettiği ile ilgili bilgi sahibiydi. Wang ve arkadaşlarının yaptığı çalışmada sigara içmenin Ig A nefropatisi ilerleyişi için önemli bir risk faktörü olduğu gösterilmiştir (48). Daha ileri analizler, sigara içmenin daha şiddetli tübüler atrofi/interstisyel fibrozis ile ilişkili olduğunu göstermiştir. Sigara içmek oksidatif stresi indükleyebilir ve merkezi damarların sertliğini artırabilir, tübüler hasara neden olabilir ve tübüler atrofi ve fibroz riskini artırabilir (49,50). Aynı zamanda sigara akciğer enfeksiyonlarını da kötüleştirebilir. Leung ve ark.sigara içmenin Covid-19 ile ilişkili pnömoni için önemli bir risk faktörü olduğu sonucuna varmıştır (51). Aynı zamanda FeiRanGuo tarafından güncellenmiş bir meta-analizde, sigara içmenin Covid-19'un ciddiyeti ile bağlantılı olduğu belirlendi (52). Ek olarak, Hu ve ark. sigara içmenin Covid-19'un olumsuz klinik sonuçları ile ilişkili olduğunu göstermiştir (53). Bizim öngörümüz sigara içme oranı az olan eğitimli hastalarda Covid-19'a bağlı komplikasyonların daha az olacağı yönündeydi ama sonuçlar bununla uyumlu gelmedi. Çalışılan hasta grubunun azlığı bunda etkili olmuş olabilir.

Çalışmamızda eğitimli grupta daha fazla favipravir kullanımı olduğunu tespit ettik (%84vs%22, p=0,026).Favipiravirin etkisini in vitro inceleyen Çinli araştırmacılar, favipiravirin viral replikasyonu azaltmada etkili olduğunu buldular (54). Bir çalışmada Favipiravirin, Covid-19 ile ilgili olarak etkin bir tedavi sağlamak, mortaliteyi azaltmak ve erken taburculuğu sağlamak için çok önemli olabileceği gösterilmiştir (55). Manabe ve arkadaşlarının derlediği bir metaanalizde özellikle hafif-orta şiddette Covid-19 hastalarında favipiravirin 7 gün içinde viral klirensi ve 14 gün içinde klinik iyileşmeyi destekleyebileceğini ortaya koymuştur. Favipiravir ile tedaviye erken başlanması, Covid-19 için olumlu sonuçlara katkıda bulunabiliceği gösterilmiştir (56). Ancak 2021 yılının Kasım ayında yapılan PRESECO çalışmasında favipiravir kullanımının etkisiz olduğu bulunmuştur (57). Her ne kadar şu an favipravirin Covid-19 tedavisinde etkisiz olduğu gösterilmiş olsa da bizim çalışma yaptığımız dönemde ana ilaçlardan biriydi. Eğitimli grupta bu ilacın kullanımının daha fazla olması bize eğitimin ilaç kullanımındaki etkisini göstermektedir. Çünkü eğitim almayan kişiler muhtemelen sosyal medyadan, çevredeki favipiravirin öldürdüğü, kısır bıraktığı yönündeki dedikodulardan etkilenerek ilacı kullanmamış olabilir. Her ne kadar favipravir etkili değilse de önemli olan hasta ve hekim arasındaki güven ve işbirliğidir. Önemli olan hastaların güncel önerilere uymalarıdır. Bu uyum eğitim grubumuzda fazla çıkmıştır.

Eğitimli grupta Covid-19 sonrası yaşayan hastalarda rutin HD ihtiyacının daha az olabileceğini öngörmüştük. Çalışma sonucunda eğitim almayan gruptaki hastaların Covid -19 geçirdikten sonra %17,6'sının rutin hemodiyalize bağlandığı görüldü. Eğitim alan grupta %6,3 ile bu oran daha az olmakla birlikte istatistiksel olarak anlamlı fark saptamadık (p<0,07). Bu durum yine hasta sayımızın azlığından kaynaklanıyor olabilir. Daha fazla hasta sayısında belki bu fark istatistiksel anlamlı hale gelebilir. Önceki çalışmalar, multidisipliner prediyaliz hasta eğitiminin evre 4-5 KBY hastalarında diyaliz insidansını ve mortaliteyi azalttığını göstermiştir (58). Ek olarak başka bir çalışmada prediyaliz hasta eğitimi, KBY hastaları arasında acil diyaliz ve kardiyovasküler olaylar açısından daha iyi klinik sonuçlarla ilişkilendirilmiştir (59).

Covid-19 geçiren hastalarda elektrolit bozukluğu, akut böbrek yetmezliği, kronik böbrek yetmezliğinde ilerleme gibi komplikasyonların görülebileceği çeşitli çalışmalarda bildirilmiştir (60). Çalışmamıza laboratuvar bulguları olarak bakıldığında Covid-19 geçirdikten sonra yaşayan hastalarda eğitim almayan grupta üre (101 vs105.5, p=0.04) ve kreatin artışı olduğu (3.8 vs 3.97, p=0.004) ve glomeruler filtrasyon hızında (GFR) azalma (20.24 vs 14.55, p=0.014) olduğu görüldü. Eğitim almayan katılımcılarda fosforda artış olduğu görüldü (4.25 vs4.9, p=0.043). Ancak aksine eğitim alan grupta kreatininde azalma (3.16 vs 2.93, p=0.004) ve glomeruler filtrasyon hızında artış (19.85 vs 20.44, p<0.001) olduğu görüldü, görece anlamlı olmasa da istatistiksel olarak anlamlıdır. Daha önce yapılan çalışmalarda prediyaliz hasta eğitiminin KBY evresinden bağımsız olarak GFR düşüşünü yavaşlattığı, acil diyaliz ihtiyacını azalttığı ve SVO, MI gibi herhangi bir morbidite gelişimini azalttığı gösterilmiştir (61-63). 2018 yılında yayınlanan 21 çalışmayı içeren bir meta analizde KBY hastalarında hasta eğitiminin glomeruler filtasyon hızında azalmayı yavaşlattığı, geçici diyaliz riskini azalttığı, hastaneye yatış oranını azalttığı ve tüm nedenlere bağlı ölüm riskini azalttığı gösterilmiştir (30). Eğitimli grupta Covid-19 geçirdikten sonra hemoglobinde düşüş olduğu görülmüştür. Bu durumun eğitimli hastalarımıza önerdiğimiz katı diyet kaynaklı olabileceğini düşünmekteyiz. Covid-19'da sepsis, şok, sitokin hasarı, kardiyorenal organ hasarı, hipoksi, sıvı-elektrolit bozukluğu, perfüzyonun azalması, rabdomiyolize bağlı tübüler toksisite ve endotoksin gibi birçok faktör ABH'ye sebep olabildiğini daha önce belirtmiştik (64). Bu durumlar nedeniyle hastada halihazırda mevcut olan KBY evresinin daha da ilerleyebileceği öngörülmektedir. Bu şekilde immün sistemi güçlü olmayan hastaların böbrek

fonksiyonlarında bozulma olabileceğini düşünmekteyiz. Ancak doğru ve uygun beslenme kurallarını ve yaşam tarzı değişikliklerini öğrenmek, her aşamada KBY olan hastalar için hayati önem taşır. Hastalar, doğru yiyecek ve içecekleri tüketerek; sodyum, potasyum ve fosfordan kaçınarak, immün sistemin güçlenmesini sağlayacak beslenme programlarına uyarak KBY 'ye bağlı bazı sağlık sorunlarını önleyebilir veya KBY ilerlemesini geciktirebilir.[40] Bu durumla uygun olarak tarafımızca verilen hasta ve bakıcı eğitimi, yaşam tarzı değişiklikleri, beslenme ve düzenli egzersiz, doğru dozlarda doğru ilaçların kullanımı, moral ve motivasyon desteği, sıvı dengesi ayarı, rezidü böbrek fonksiyonlarını koruma ve nefroprotektif alternatif tıp tedavileri gibi prediyaliz hasta eğitimi sayesinde eğitimli grubumuzda Covid-19 geçirdikten sonra kreatininde düşüş, GFR'de artış meydana geldi. Diğer bir deyişle böbrek fonksiyonlarında iyileşme meydana geldi. Aslında Covid-19 gibi ciddi komplikasyonlara yol açan bu ölümcül virüsü geçiren hastalarda eğitimli olsa bile az bir oranda böbrek fonksiyonlarında bozulma beklerdik. Ayrıca eğitimli grupta Covid-19 öncesi bakılan laboratuvar değerleri hastalıktan median 80 gün önce bakıldığı halde hastalıktan median 73 gün sonra böbrek fonksiyonlarında düzelme olması ilginçtir. Çünkü KBY doğası gereği ilerleme eğiliminde olan bir hastalıktır. Halbuki bizim hastalarımızda verdiğimiz eğitim sayesinde böbrek fonksiyonlarında düzelme izlenmiştir. Ayrıca eğitimli hastalar; immün sistemi güçlendiği düşünülen hastalar olmasının yanında bu pandemi sürecinde hastalığa yakalandıktan ve hastalığı atlattıktan sonra beslenme konusunda daha da dikkatli davrandıkları için böbrek fonksiyonlarında düzelme meydana gelmiş olabilir.

Eğitimli grubun hastane yatış ve komplikasyonlarının her ne kadar daha az olmasını beklediysek de sonuçtaher iki grupta da hastaneye yatış durumu, yatış süresi, ev, yataklı servis veya yoğun bakımda yatış farkı, entübasyon oranı, miyokard enfarktüsü veya serebrovasküler olay gibi morbidite gelişimi, mortalite oranı, seyirde geçici hemodiyaliz ihtiyacı ve hastalığı geçirdikten sonra rutin hemodiyaliz ihtiyacı gibi durumlar arasında fark gözlemleyemedik. Bunun sebebi hasta sayımızın az olmasında kaynaklanıyor olabilir. Literatürde bununla ilgili herhangi bir çalışma olmadığı için karşılaştırma yapamadık. Bu konuyla ilgili literatüre katkı yapan ilk çalışma olmaktayız.

Dünyada 2021 yılı şubat ayı itibariyle Covid-19'a karşı birçok farklı aşı kullanıma sunulmuştur. Bunlar mRNA aşıları olan Pfizer-Biontech ve Moderna aşıları, adenovirüs aracılığıyla üretilen Janssen-Johnson & Johnson, AstraZeneca, Sputnik-V ve Casino vektörel aşılardır. TURKOVAC, Bharat Biotech ve Sinovac aşıları ise inaktive SARS-CoV- 2 aşılarıdır. Ülkemizde Pfizer-Biontech, Sinovac ve TURKOVAC aşıları 2021 Şubat ayından itibaren yapılmaya başlanmıştır. Aşıların Covid-19 enfeksiyonunu önleme, hastalığa yakalanma durumunda morbidite ve mortaliteyi azaltmada çeşitli oranlarda etkileri bilinmektedir (65). Biz çalışmamıza sonuçları etkileme ihtimali nedeniyle herhangi bir Covid-19 aşısı olmuş olan bireyleri almadık.

Çalışmamızın retrospektif dizayn olması, hastaneye yatan hastaların farklı hastanelerde farklı hekimler tarafından takip edilmesi, hastalığın şiddeti ve uygulanan ek ilaçlar hakkında bilgimizin olmaması, tarafımıza kontrole gelemeyen bazı hastalara ulaşamamamış olmak (vefat vs.) negatif yönleriydi. Böylece gerçekte sayıca fazla olandan daha az sayıda hasta tespit edilmiş olabilir.

SONUÇ

Çalışmamızda prediyaliz KBY hasta eğitiminin Covid-19 sonrası gelişebilecek renal fonksiyon kaybına sebep olmadığını hatta böbrek fonksiyonlarında iyileşme sağladığını gösterdik. Ayrıca eğitim alan grupta favipiravir kullanımın daha fazla olduğunu ve sigara

kullanımın daha az olduğunu gördük. İki grup arasından eğitimi olmayan grupta Covid-19 sonrası üre, kreatinin ve fosfor düzeylerinde artma, GFR'de azalma olduğunu gördük. Eğitimli olan grupta ise Covid-19 sonrası kreatininde azalma ve GFR'de artma, hemoglobinde düşme olduğunu gördük. Her iki grupta hastaneye yatış, yatış süresi, entübasyon oranı, hastalık seyrinde morbidite ve mortalite gelişimi, seyirde geçici hemodiyaliz ihtiyacı ve hastalık sonrası rutin hemodiyaliz gereksinimi arasında fark saptamadık. Bu durum hasta sayısının az olmasında kaynaklı olabilir. Literatürde, prediyaliz hasta eğitimiyle Covid-19'un böbreklere olan etkisini araştıran herhangi bir çalışma bulunmamaktadır. Bu nedenle bu çalışmamızın bu konu ile ilgili yapılacak diğer çalışmalara öncü olacağını düşünmekteyiz.

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Yazar Katkıları

Çalışma Konsepti / Tasarımı	**:** BÖ, ÖT
Veri Toplama	**:** BÖ
Veri Analizi / Yorumlama	**:** BÖ, ÖT
Yazı Taslağı	**:** BÖ, ÖT
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İçeriğin Eleştirel İncelemesi	**:** ÖT
Literatür Taraması	**:** BÖ

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Elastofibroma Dorsi ile Dominant El Kullanımının ilişkisi var mı?

Is there a relationship between Elastofibroma Dorsi and Dominant Hand Use?

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Özet

Giriş: Elastofibroma Dorsi göğüs duvarından kaynaklanan benign tümörlerdir. Etyolojisinde kol kullanımına bağlı olarak skapula margo inferiorunun yarattığı mikrotravmalar suçlanmaktadır.
Amaç: Çalışmamızda opere ettiğimiz Elastofibroma Dorsi vakalarının boyutsal progresyonu ve dominant el kullanımıyla ilişkisini değerlendirmeyi amaçladık.
Yöntem: Kliniğimizde Ocak 2018 ve Ocak 2023 tarihleri ED nedeniyle opere olan hastalar yaş, cinsiyet, semptom, yön, meslek, nüks, komorbiditeler, lezyon boyutları ve gelişen komplikasyonlar retrospektif olarak incelendi. Tüm hastalara operasyon öncesi Manyetik Rezonans görüntüleme yapılarak radyolojik tanı konuldu ve sonra prone pozisyonunda genel anestezi altında supscapuler alanda yapılan posterior torakotomi insizyonuyla opere edildi. Seroma ve hematomu önlemek amacıyla günlük sıkı pansumanları yapıldı. Drenaj 25 mL/d altında drenler alındı.
Bulgular: Yaş ortalaması 57,81±7,50 olan 31(83.2%) kadın, 6(16.2%) erkek hasta çalışmaya alındı. 30 (%81,1) hasta ev hanımı, 6 (%16,2) el işi ile çalışan ve 1 (%2,7) kişi de öğretmendi. Kitlelerin 31 (%83,8)'i bilateral, 5 (%13,5)'i sağ taraflı, 1 (%2,7)'i sol taraflıydı. Hastaların 33 (%89,2)sinde dominant el sağ, 4 (%10,8)'ünde sol idi. Semptom olarak 27 (%73,0) hastada ağrı, 17 (%45,9) hastada şişlik, 5 (%13,5) hastada hareket kısıtlılığı saptandı. 3 (%8,1) hasta nüks nedeniyle tekrar opere edildi. Sağ taraflı kitlelerin ortanca hacmi 171,5(91,5-252,9) ve sol taraflı kitlelerin ortanca hacmi 150,0 (55,8-229,3) olarak hesaplandı. Sağ - sol baskın el ve kitle hacimleri arasındaki karşılaştırmada ise istatistiksel anlamlı farklılık saptanmadı (sırasıyla p=0,942, p=0,361).
Sonuç: Çalışmamızda ED boyutu ve dominant el kullanımı arasında bir ilişki saptanamamıştır. Fakat ED'li hastalarımızın çoğu istatistiksel anlamlı olarak ellerini kullanarak çalışan işçilerdi. Olgu sayısı daha fazla çalışmalar ile daha farklı sonuçlar elde edilebilinecektir.

Anahtar Kelimeler: Elastofibroma Dorsi, Göğüs Duvarı Tümörü, Dominant EL.

Abstract

Introduction: Elastofibroma Dorsi (ED) are benign tumors arising from the chest wall. Microtraumas caused by the scapula margo inferior due to arm use are blamed for its etiology.
Objectives: In our study, we aimed to evaluate the dimensional progression of the Elastofibroma Dorsi cases we operated and its relationship with dominant hand use.
Method: Patients who were diagnosed as ED between January 2018 and January 2023 were retrospectively evaluated in terms of age, gender, symptoms, side, job, recurrence, comorbidities, lesion sizes and complications. All patients were diagnosed radiologically by Magnetic Resonance imaging before the operation, and then a posterior thoracotomy incision was made in the suscapular area under general anesthesia at the prone position. Tight dressings were applied daily to prevent seroma and hematoma. If the drainage was below 25 mL/d, drains were removed.
Results: 31(83.2%) female and 6(16.2%) male patients with an average age of 57.81±7.50 were included in the study. 30 (81.1%) patients were housewives, 6 (16.2%) were manual workers and 1 (2.7%) was a teacher. 31

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(83.8%) of the lesions were bilateral, 5 (13.5%) were right-sided, and 1 (2.7%) was left-sided. The dominant hand was right in 33 (89.2%) of the patients and left in 4 (10.8%). Symptoms were pain in 27 (73.0%) patients, swelling in 17 (45.9%) patients, and limitation of movement in 5 (13.5%) patients. 3 (8.1%) patients were re-operated due to recurrence. The median volume of right-sided masses was calculated as 171.5 cc (91.5-252.9) and the median volume of left-sided masses was 150.0 cc (55.8-229.3). No statistically significant difference was detected in the comparison between right and left dominant hand and mass volumes (p=0.942, p=0.361, respectively).

Conclusion: In our study, no relationship was found between ED size and dominant hand use. However, statistically significant majority of our patients with ED were workers using their hands. Different results can be obtained with studies with more cases.

Keywords: Elastofibroma Dorsi, Chest Wall Tumors, Dominant Hand Use.

GİRİŞ

Elastofibroma Dorsi (ED) fibröz dokudan kaynaklanan, subskapular bölgeye yerleşen, yavaş büyüyen, kapsülsüz, benign tümörlerdir (1). Etyolojisinde kol hareketlerine bağlı olarak skapula alt ucunun yarattığı mikrotravmalar belirtilse de sebebi tam olarak belli değildir (2). Bazı otopsi araştırmalarında ise ED'nin yaşlanmanın bir sonucu olduğu da belirtilmiştir (3).

Elli beş yaş üstü kadın popülasyonda ve tek taraflı görülme sıklığı fazladır (4). %10 oranında bilateral olarak izlenirler (5). Genelde asemptomaik olarak rastlantısal olarak saptansa da şişlik, ağrı ve takılma hissi gibi semptomlar verebilmektedirler (6).

Tanıda radyolojik incelemeler yeterli olarak görülse de maligniteyi dışlamak amacıyla doku tanısı önerilmektedir. Semptomatik olan ve/veya büyük boyutlu olgularda ise hem tanı hem de tedavi amacıyla marjinal rezeksiyon önerilmektedir (7).

Çalışmamızda kliniğimizde opere ettiğimiz vakaları değerlendirdik. Etyolojisinde üst ekstremite kullanımına bağlı oluşan mikrotravmaların suçlandığı ED'nin boyutsal progresyonu ve dominant el kullanımıyla ilişkisini değerlendirmeyi amaçladık.

YÖNTEM

Kliniğimizde Ocak 2018 ve Ocak 2023 tarihleri ED nedeniyle opere olan hastalar dahil edildi. Hastaların yaş, cinsiyet, semptom, yön, meslek, nüks, komorbiditeler, lezyon boyutları ve gelişen komplikasyonlar retrospektif olarak incelendi.

Hastalara operasyon öncesi Manyetik Rezonans görüntüleme yapılarak radyolojik tanı konuldu. Tüm hastalar prone pozisyonunda genel anestezi altında opere edildi. Supscapuler alanda yapılan posterior torakotomi insizyonu ile latismus dorsi kası altına girildi ve kitle total eksize edildi. Kanama kontrolü ardından 1'er adet dren konularak işleme son verildi. Seroma ve hematomu önlemek amacıyla günlük sıkı pansumanları yapıldı. Drenaj 25 mL/d altında drenler alındı.

İstatistiksel Analizler

Veriler SPSS (Statistical Package for the Social Sciences Versiyon 22.0; SPSS Inc. Chicago, IL, ABD) yazılım paketi ile analiz edildi. Parametrik olmayan verilerin ortalama değeri, 25 ve 75 yüzdelikleri ile kategorik değişkenlerin sayısal değerleri ve yüzdeleri tanımlayıcı istatistik olarak hesaplandı. Kategorik değişkenler arasındaki ilişki Ki-kare ve Fisher's exact testleri ile, parametrik olmayan veriler ile kategorik değişkenler arasındaki ilişki ise Mann-Whitney U testi ile incelenmiştir. Tüm analizlerde $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Yaş ortalaması 57,81±7,50 olan 31(83.2%) kadın, 6(16.2%) erkek toplam 37 hasta çalışmaya alındı. 30 (%81,1) hasta ev hanımı, 6 (%16,2) el işi ile çalışan ve 1 (%2,7) kişi de öğretmendi. Hastaların 21 (%56,8)'inde ek hastalık mevcuttu. Kitlelerin 31 (%83,8)'i bilateral, 5 (%13,5)'i sağ taraflı, 1 (%2,7)'i sol taraflıydı. Hastaların 33 (%89,2)sinde dominant el sağ, 4 (%10,8)'ünde sol idi.

Tablo 1. Demografik Bilgiler

		n (%)
Yaş		57,81±7,50*
Cinsiyet	Erkek	6 (%16,2)
	Kadın	31 (%83,8)
Çalışma Durumu	Çalışmıyor	30 (%81,1)
	Aktif Çalışıyor	7 (%18,9)
Baskın El	Sağ El	33 (%89,2)
	Sol El	4 (%10,8)
Eşlik Eden Komorbidite Durumu	Komorbidite Yok	16 (%43,2)
	Komorbidite Var	21 (%56,8)
Semptom	Ağrı	27 (%73,0)
	Şişlik	17 (%45,9)
	Hareket Kısıtlılığı	5 (%13,5)
Taraf	Sağ	5 (%13,5)
	Sol	1 (%2,7)
	Bilateral	31 (%83,8)
Sağ Kitle Hacmi		171,5(91,5-252,9)**
Sol Kitle Hacmi		150,0(55,8-229,3)**
Komplikasyon Durumu	Komplikasyon Yok	34 (%91,9)
	Hematom	1 (%2,7)
	Seroma	2 (%5,4)
Relaps Varlığı	Relaps Yok	34 (%91,9)
	Relaps var	3 (%8,1)

n: sayı, *ortalama±SS, **medyan (25.-75.persantil).

Semptom olarak 27 (%73,0) hastada ağrı, 17 (%45,9) hastada şişlik, 5 (%13,5) hastada hareket kısıtlılığı saptandı. 34 (%91,9) hastada postoperatif dönemde komplikasyon saptanmazken 2 (%5,4) hastada seroma, 1 (%2,7) hastada hematom saptandı ve ponksiyon ile giderildi. 3 (%8,1) hasta nüks nedeniyle tekrar opere edildi.

Sağ taraflı kitlelerin ortanca hacmi 171,5(91,5-252,9) ve sol taraflı kitlelerin ortanca hacmi 150,0(55,8-229,3) olarak hesaplandı. Ev hanımları ve diğer çalışanlar arasında yapılan karşılaştırmada ev hanımı olmayan hastalarda sol taraflı kitle boyutları istatistiksel olarak anlamlı bulundu (p=0,029). Cinsiyet kıyaslamasında ise erkeklerde sol taraflı kitle boyutları anlamlı olarak daha büyüktü (p=0,005).

Sağ - sol baskın el ve kitle hacimleri arasındaki karşılaştırmada ise istatistiksel anlamlı farklılık saptanmadı (sırasıyla p=0,942, p=0,361). Semptom açısından bakıldığında ise ağrı, şişlik ve hareket kısıtlılığı açısından sağ ve sol kitle boyutları arasında anlamlı bir boyut farkı saptanmadı. Aynı şekilde komplikasyon ve nüks açısından da sağ ve sol kitle boyutları açısından anlamlı istatistiksel fark saptanmadı (Tablo 2).

Tablo 2. Sağ Ve Sol Kitle Ortanca Hacimleri Ve Çeşitli Parametreler Arasındaki İlişkiler

			Sağ Kitle Hacmi (medyan(25.-75))	p	Sol Kitle Hacmi (medyan(25.-75))	p
Cinsiyet	Erkek		270,0(176,0-450,0)	0,058	330,0(218,5-371,5)	**0,005**
	Kadın		164,7(82,5-234,4)		116,8(43,2-196,0)	
Çalışma Durumu	Ev Hanımı		164,7(82,5-234,4)	0,058	116,8(43,2-196,0)	**0,029**
	Diğer		270,0(176,0-450,0)		330,0(218,5-371,5)	
Baskın El	Sağ El		170,1(91,5-252,9)	0,942	150,0(47,4-213,3)	0,361
	Sol El		197,5(111,4-2715)		192,4(120,9-287,5)	
Semptom	Ağrı	Yok	145,1(49,9-247,8)	0,565	96,5(9,4-212,5)	0,229
		Var	189,0(110,8-252,9)		156,0(69,0-229,3)	
	Şişlik	Yok	142,6(80,2-261,5)	0,369	88,5(47,4-163,1)	0,080
		Var	176,0(145,1-252,9)		196,0(127,5-287,5)	
	Hareket Kısıtlılığı	Yok	173,8(83,3-252,9)	0,690	144,9(47,4-242,5)	0,760
		Var	144,0(133,3-234,0)		157,5(143,0-168,8)	
Komplikasyon Durumu	Komplikasyon Yok		170,1(84,0-270,0)	0,347	139,8(51,6-218,5)	0,363
	Komplikasyon Var		205,9(176,0-235,9)		243,0(156,0-330,0)	
Relaps Varlığı	Relaps Yok		173,8(110,8-252,9)	0,717	147,9(55,8-229,3)	0,473
	Relaps Var		183,5(63,0-304,0)		215,0(15,0-280,0)	

TARTIŞMA

ED benign, fibroblastik-myofibroblastik bağ dokusu tümörleridir. Tümör karakteri, seyri ve lokalizasyonu nedeniyle sarkomlar ve desmoid tümör ile karıştırılabilmektedir. Literatürde ED ile ilgili yayınlar genelde olgu sunumu ve küçük seriler halindedir. Klinikte seyrek karşımıza gelen iyi huylu yumuşak doku tümörleri olsalar da radyolojik taramalarda 2% ve otopsi serilerinde 55 yaş üstü erkeklerin %11.2'sinde kadınların %24.4'ünde saptanmıştır (4,8). Ayrıca vaka serilerinde ED kadın cinste daha fazla izlenmektedir (9). Bizim çalışmamızda da hastaların yaş ortalaması 57,81±7,50 kaydedildi. Ek olarak olgularımızın 83.2%'si kadındı. Yapılan çalışmalarda bilterallik %10-66 arasında değişmektedir (5). Çalışmamızda olguların 83.8%'si bilateraldi.

Genellikle reaktif süreçlere bağlı olarak biriken anormal elastik fiberler ile karakterize olan ED'nin etiolojisinde tekrarlayan mikrotravmalar suçlanmaktadır (10). Bu nedenle daha çok kol gücü kullanarak çalışanlarda özellikle ev hanımlarında daha fazla saptanmaktadır (11). Bizim çalışmamızdaki olguların ise 81.1%'si ev hanımı, 16.2% el gücü ile çalışan ve 1 kişi de öğretmendi. Bu da mikrotravma hipotezini desteklemekteydi.

ED'nin en sık semptomu ağrı, şişlik ve hareket kısıtlılığıdır. Hammoumi ve ark. çalışmasında 93% hastada ağrı, 51.3% hareket kısıtlılığı saptanmıştır (12). Deveci ve ark. yaptığı çalışmada ise 73.7% ağrı ve 65% hareket kısıtlılığı saptandı (11). Bizim çalışmamızda 73% hastada ağrı 45,9% hastada şişlik ve 13.5% hastada hareket kısıtlılığı belirtildi. Mevcut semptomların ameliyat sonrası tamamen gerilediği izlendi.

ED'de cerrahi endikasyonu tartışmalıdır. Çalışmalarda boyuta bakılmaksızın semptomatik tüm olguların radyolojik tanıyı desteklemek amacıyla opera edilmesi gerektiğini savunsa da, sadece çapı 5 cm'den büyük semptomatik vakaların opere edilmesi gerektiğini belirten yayınlar da mevcuttur (11,13). Şu ana kadar ED ve malign transformasyon izlenmemiştir (11). Bizim çalışmamıza katılan ED ortalama hacimleri ise 161 cm olarak saptandı ve semptomatik olan tüm olgular boyutuna bakılmaksızın opere edildi. Bazı vaka serilerinde nüksten

bahsedilmektedir (14). Bizim çalışmamızda da 3 hastada nüks izlendi. Bu hastalar tekrar opere edildi.

Operasyon sonrası oluşabilecek komplikasyonlar seroma, hematom ve yara yeri enfeksiyonudur. Postoperatif erken dönem komplikasyonlarından olan seromayı önlemek amacıyla 5 cm'den büyük tüm olgularda operasyon bitirilirken drenaj kateteri konulup kompresyon bandaj uygulandı ve drenaj en az 24 saat takip edildi. Nagano ve ark. çalışmasında 43% oranında hematom geliştiğini ve bu oranın tümör büyüklüğüyle ilişkili olduğunu belirtmiştir (13). Bizim çalışmamızda sadece 3 hastada komplikasyon gelişti. Bu düşük oranın kullandığımız drenaj kataterine, kompresyon bandaj uygulaması nedeniyle olduğunu düşünüyoruz.

Çalışmalarda sağ taraflı ED çoğunluktaydı ve bunu dominant el kullanımına bağlı oldu düşünülmekteydi (15). Fakat Tepe ve ark. çalışmasında sağ ve sol el arasında anlamlı farklılık saptanmamıştır (16). Kambur Metin ve ark.'ın çalışmasında ise dominant el ve tümör tarafı arasında anlamlı bir ilişki olduğu belirtilmiştir (17). Bizim çalışmamızda sağ ve sol taraflı kitle boyutlarının değişik parametrelerle olan ilişkisi değerlendirildi. Dominant el kullanımıyla tümör boyutu arasında ilişkili bulunmadı. Fakat erkek cinste sol taraflı kitle boyutunun istatistiksel anlamlı daha büyük olduğu görüldü. Ayrıca ev hanımlarında yine sol taraflı lezyonlar daha büyük boyutlara ulaşmaktaydı.

Çalışmanın Kısıtlamaları

Çalışmamızın kısıtlamaları; tek merkezli, ve retrospektif olmasıdır. Fakat çalışmamız dominant el ve aynı taraflı tümör boyutunun ilişkisini incelendiği İngilizce literatürdeki ek çalışmadır. Daha yüksek olgu sayılarıyla yapılan çalışmalarla daha değerli istatistiki sonuçlar alınacağı aşikardır.

SONUÇ

Sonuç olarak çalışmamızda Elastobifroma Dorsi boyutu ve dominant el kullanımı arasında ilişki saptanamamıştır. Fakat çalışmamıza dahil olan EDli hastaların büyük bir kısmını elini kullanarak çalışanlardı. İleride daha fazla olgu içeren çalışmalarda daha farklı sonuçlar çıkması mümkündür.

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Yazar Katkıları

Çalışma Konsepti / Tasarımı	: KK, CB
Veri Toplama	: KK, CB
Veri Analizi / Yorumlama	: KK, CB
Yazı Taslağı	: KK, CB
Teknik Destek / Malzeme Desteği	: KK, CB
İçeriğin Eleştirel İncelemesi	: KK, CB
Literatür Taraması	: KK, CB

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The 24 Big Challenges of Artificial Inteligence Adoption in Healthcare

Sağlıkta Yapay Zeka Uygulamasının 24 Büyük Zorluğu

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Abstract

Introduction: The integration of Artificial Intelligence (AI) into medical disciplines has shown significant potential. However, while an abundance of literature is enthusiastic about the potential and promises of AI, particularly in medical diagnostics, there is a distinct of discussion concerning the multitude of challenges associated with its widespread adoption in practical medical settings.
Objective: This study aims to thoroughly analyze the challenges associated with adopting artificial intelligence technologies in medical practice. It provides a realistic perspective on the progress of this technology, countering the often overly idealized viewpoints that primarily showcase advancements in prototypes and technological demonstrators within controlled laboratory conditions.
Method: The research design of this study is grounded in the method of document analysis/review. In this context, numerous scientific works were explored through platforms such as Google Scholar, PubMed, BioMed Central, Cochrane, and various scietific databases. Access to articles was obtained, followed by meticulous data analysis and assessments. Search criteria were adjusted based for each of the challenges under examination.
Results:A total of 24 significant challenges have been identified, intricately interconnected, and dissected using examples that illustrate the maturity level of AI-based developments within the medical domain. These challenges have been categorized into three main categories based on their nature. Each section has been wriiten in a way that can be independently comprehended. The future holds great promise, as underscored by numerous articles showcasing the remarkable advancements arising from the synergy between medicine and artificial intelligence. Hence, there is a need to develop critical thinking to discern the benefits, current limitations, and new paths to overcome them.
Conclusion: None of the challenges holds greater importance than the others. The evolution of artificial intelligence in medicine entails collectively overcoming these challenges, using strategies to maximize benefits for both patients and medical experts.

Keywords: Artificial Intelligence, Radiology, Learning Curve, Deep Learning, Health Centers.

Özet

Giriş: Yapay Zeka'nın (YZ) tıbbi disiplinlere entegrasyonu önemli bir potansiyel göstermiştir. Ancak, AI'ın potansiyeli ve vaatleri hakkında coşkulu bir literatür bolluğu olmasına rağmen, özellikle tıbbi teşhislerde, pratik tıbbi ortamlarda yaygın olarak benimsenmesiyle ilişkilendirilen birçok zorluk hakkında tartışma eksikliği vardır.
Amaç: Bu çalışma, tıbbi uygulamada yapay zeka teknolojilerini benimseme ile ilişkilendirilen zorlukları ayrıntılı olarak analiz etmeyi amaçlamaktadır. Bu teknolojinin ilerlemesi hakkında gerçekçi bir perspektif sunar, kontrol altındaki laboratuvar koşullarında prototiplerin ve teknolojik göstericilerin ilerlemesini öne çıkaran aşırı idealize edilmiş görüşlere karşı koyar.
Yöntem: Bu çalışmanın araştırma tasarımı, belge analizi/inceleme yöntemine dayanmaktadır. Bu bağlamda, Google Scholar, PubMed, BioMed Central, Cochrane ve çeşitli bilimsel veritabanları gibi platformlar aracılığıyla

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birçok bilimsel çalışma keşfedildi. Makalelere erişim sağlandı, ardından dikkatli veri analizi ve değerlendirmeleri yapıldı. İncelenen her zorluk için arama kriterleri ayarlandı.
Bulgular: Toplamda 24 önemli zorluk tespit edildi, bunlar iç içe geçmiş ve tıbbi alandaki AI tabanlı gelişmelerin olgunluk seviyesini örneklendiren örneklerle ayrıntılı olarak incelendi. Bu zorluklar doğalarına göre üç ana kategoriye ayrılmıştır. Her bölüm, bağımsız olarak anlaşılabilir bir şekilde yazılmıştır. Gelecek, tıp ve yapay zeka arasındaki sinerjiden kaynaklanan dikkat çekici ilerlemeleri vurgulayan sayısız makale ile büyük vaatlerde bulunmaktadır. Bu nedenle, faydaları, mevcut sınırlamaları ve bunların üstesinden gelmek için yeni yolları ayırt edebilmek için eleştirel düşünmeyi geliştirmek gerekmektedir.
Sonuç: Zorlukların hiçbiri diğerlerinden daha önemli değildir. Tıpta yapay zekanın evrimi, hem hastalar hem de tıbbi uzmanlar için faydaları en üst düzeye çıkarmak için stratejiler kullanarak bu zorlukların kolektif olarak üstesinden gelinmesini gerektirir.

Anahtar Kelimeler: Yapay Zeka, Radyoloji, Öğrenme Eğrisi, Derin Öğrenme, Sağlık Merkezleri.

INTRODUCTION

The integration of Artificial Intelligence (AI) into medical disciplines has shown significant potential. However, while an abundance of literature is enthusiastic about the potential and promises of AI, particularly in medical diagnostics, there is a distinct of discussion concerning the multitude of challenges associated with its widespread adoption in practical medical settings (1).

Research prototypes and technological demonstrators –usually shown by researchers from academic institutions and startup enterprises– are considerably different from full-fledged, operational systems in active clinical environments. Medical practice requires that any technological adjunct to it, AI-based or otherwise, adheres to strict standards of design, planning, and validation. Such observance ensures that these systems not only augment the abilities of medical professionals but do so in a manner as reliable as any certified medical equipment (2).

This paper provides a comprehensive exploration of 24 significant challenges that are intrinsic to the adoption of AI technologies in healthcare. These challenges are catalogued into three main themes: eight associated with the development of software AI-based solutions; another eight linked to their adaptation, integration, and operation within existing healthcare facilities; and the final eight focusing on the ethical, societal, and equality implications in healthcare access. We must that each challenge is complex enough to be the subject of an independent research article. This review, however, aims to offer a balanced andcomprehensiveexploration of the real-world intricacies facing the deployment of AI solutions in clinical practices. While the merits of AI have been highlighted in a prior research work (3) published in this journal, the rate at which these advantages mature into accessible solutions for clinicians appears more restrained.

It is not surprising that Mr. Sayar, in his recent article titled "Use of Artificial Intelligence in Medicine" (3), has focused his attention on the technological advancements impacting the field of Radiology. The recent advances in computational vision and the evolution of Deep Learning have synergistically elevated Radiology's potential for enhanced diagnostics and treatment planning (4). The discipline's intrinsic dependence on imaging has always encouraged a close relationship with evolving computational technologies (5). Nevertheless,

the journey from a proof-of-concept algorithm in a controlled environment to an operationally reliable tool in diverse clinical settings is riddlewith a range of complex challenges. The realization of AI's potential in medicine is not simply a matter of technological advancement but also involves skilful manoeuvring through the complexities of software development, deep learning training, the peculiarities of healthcare operations, and ethical considerations.

The software development for AI in healthcare is not merely a replication of traditional software engineering. The vast and diverse data requirements, the need for interpretability, and the twists and turns of deploying machine learning models in production are unique and demand special attention (6). Furthermore, within the security of healthcare facility, the integration of AI solutions requires the seamless merger with legacy systems, the guarantee of uninterrupted operation, and provisions for regular updates without compromising patient care.

Moreover, the potential for AI to reshape healthcare is not solely technological; it is deeply societal. The questions of who benefits from AI, how it impacts the patient-doctor relationship, and how it might inadvertently exacerbate health disparities are of paramount importance (7). These considerations ensure that the technology remains a tool for equitable healthcare advancement and doesn't devolve into a source of fragmentation or disparity.

Artificial intelligence, therefore, has shown significant potential in shaping the future of healthcare, with impacts spanning across diagnostics and personalized medicine. However, it should be noted that these potential benefits come with a set of challenges and ethical considerations. Therefore, while the promise of artificial intelligence in healthcare is substantial, careful consideration and management of these challenges are necessary in order to fully realize its potential.

HEALTHCARE AI TECHNOLOGICAL DEVELOPMENT CHALLENGES

The first section is focused on the 8 challenges related to the development of artificial intelligence applications in the field of medicine. While some of these challenges are common to all types of software built on Deep Learning algorithms, the majority are deep-rooted to the medical domain, given the sensitivity of patient data and their potential ailments.

Voracity of large and curated datasets for Deep Learning medical algorithms

Datasets are the raw material to build deep learning algorithms, their availability, size, and quality fundamentally shape the performance of these models. As remarked by Mr. Sayar (3), one salient example is the field of medical imaging, where large datasets of curated images are used to train machine learning models to detect and diagnose disease, improving both speed and accuracy over human examination alone (8). The impact of deep learning algorithms on medical diagnosis, prognosis, and treatment planning is currently being widely studied and acknowledged across the globe (9). However, the production and acquisition of large, high-quality and labelled datasets, particularly in healthcare, are fraught with challenges that slow the pace of development and the application of these powerful technologies.

Data is often scarce in healthcare settings due to factors including but not limited to data privacy regulations, the nature of rare diseases, and the gradual pace of public medical research data generation. Given that deep learning models require large amounts of data to accurately learn and predict outcomes, scarcity poses a significant challenge. Privacy regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in Europe, restrict the use and sharing of medical data, further limiting its availability (10). The development and maintenance of large databases require extensive resources, making it particularly challenging for rare diseases where data is inherently limited (11) (see section 0).

Medical data is also typically unlabelled, which necessitates the laborious task of manually annotating the data. A team of professionals with medical expertise is required to ensure accurate annotation, which can be a lengthy and costly process. Unlike other fields, healthcare data cannot be crowd-sourced due to its specialized nature and privacy concerns. Thus, the labelling process becomes a bottleneck in the use of deep learning for healthcare applications (4).

The value of curated datasets, which have been carefully collected, cleaned, and labelled, cannot be emphasized enough. However, their creation involves a significant investment of time, effort, and expertise. The benefit is twofold: high-quality datasets improve the performance of individual algorithms, and they allow researcher to advance the field as a whole by providing benchmarks against which new algorithms can be compared. This standardization, achieved through the use of curated datasets, propels forward the development of deep learning applications in medicine (12).

Despite these challenges, the healthcare field has seen some notable successes in the acquisition of medical data. Institutions like the Stanford School of Medicine, the Massachusetts General Hospital, and the Mayo Clinic, among others, have been successful in building large databases. Public datasets such as the MIMIC-III (Medical Information Mart for Intensive Care III), which contains de-identified health data associated with over forty thousand patients, or EchoNet-LVH dataset, which includes 12,000 labeled echocardiogram videos and human expert annotations (measurements, tracings, and calculations) to provide a baseline to study cardiac chamber size and wall thickness, are serving as significant sources for deep learning research (13–16).

The procurement of large and curated datasets will be a persistent challenge in the application of deep learning algorithms in healthcare, but it is a hurdle that can and must be overcome. It will take concerted effort and cooperation among multiple stakeholders, including medical institutions, regulatory bodies, and technology companies. As this issue continues to be addressed, the healthcare field will be poised to reap the full benefits of deep learning technologies.

Data quality and integrity, a prerequisite for the development of reliable AI models

The development of trustworthy artificial intelligence models in healthcare heavily relies on data quality and integrity (17). While this factor might seem self-evident, its implementation

in practice proves to be a challenge. Although most Deep Learning systems are slightly robust to noise, the well-known 'garbage in, garbage out' principle serves as a reminder of how crucial high-quality data is in influencing the performance of AI systems. This factor Is especially important in critical sectors, like Healthcare, as performance of AI systems is directly influenced by the quality of the input data (18). Thus, the task of ensuring the cleanliness, completeness, and representativeness of health data is both a significant challenge and an essential area for improvement.

Clinical data is the primary source of information for health-focused AI applications. This kind of data, derived from a variety of sources including electronic health records, clinical trials, or digital wearables, is often fragmented and laden with noise, biases, or errors. The fragmentation issue arises due to the disparate nature of health data sources, each carrying their own unique structure and format (19). Merging these disparate data sources into a cohesive whole that can be used by an AI model often requires substantial cleaning and reformatting efforts.

The presence of noise, biases, or errors introduces additional complexities. These inaccuracies can act as confounders, impeding the generalizability of AI models and potentially leading to flawed predictions. The noise in data may arise due to measurement errors, data entry mistakes, or even inherent biological variability (20). Biases can be introduced during the data collection process, often stemming from the population sample, the study design, or the collection method itself (21). Data errors, on the other hand, can arise from a variety of reasons, including data entry mistakes, transmission errors, or missing data (22).

For these reasons, several approaches are usually undertaken to enhance data quality and integrity. Methods to address the issue of fragmentation include the development of standard data formats and structures that can facilitate data integration (23). Noise reduction techniques and validation checks can help minimize errors and ensure data accuracy (24). As for biases, robust study design and sample selection techniques can help limit their introduction in the first place, and statistical methods can help adjust for them once present.

To illustrate, The Cancer Genome Atlas (TCGA) provides an example of a successful integration of diverse data types from various sources. By standardizing data structures and formats, TCGA was able to create a rich resource for cancer genomics research (25). Similarly, the Framingham Heart Study, a longitudinal study that has been ongoing since 1948, demonstrates the effectiveness of meticulous study design and robust statistical methods in minimizing biases and ensuring the quality and integrity of data collected over time (26).

Although the task of maintaining data quality and integrity presents a substantial challenge, it is not unconquerable. The prospect of AI in healthcare hinges on the capability to confront these challenges directly, employing robust strategies and methodologies to the cleanliness, completeness, and representativeness of health data.

Lack of interpretability and transparency in AI models

Since the dawn of artificial intelligence in medicine, the methodologies for extracting meaningful patterns from medical data have experienced remarkable evolutions. In the initial stages of AI-driven medical research, considerable emphasis was placed on hand-crafting features from the data, which then served as an input to machine learning algorithms (27). This manual feature engineering required lot of effort to be designed, given the constraints of computational power and the limited understanding of algorithmic designs that could capture intricate data patterns. However, these features were often dependent on the domain knowledge and intuition of the researchers, which introduced potential biases and might have omitted significant, non-intuitive characteristics (28).

Transitioning from these early strategies, the advent of deep learning and, more specifically, deep neural networks has brought about a paradigm shift in AI approaches within the medical domain (29). These models are often categorized as "end-to-end" since they are designed to learn features directly from raw data, bypassing the often labor-intensive process of manual feature design and extraction. While such models have been shown to outperform their predecessors in numerous medical applications, such as diagnostic imaging and predictive analytics, they come with a different set of challenges and considerations.

One significant aspect of these neural models is the interpretability, or more aptly, the lack thereof (30). The features learned by deep networks tend to be more abstract and non-linear, making them more difficult to interpret in a comprehensible manner by human researchers. This raises questions about transparency, trustworthiness, and the very nature of knowledge in AI-driven medical applications. While these models provide results with high accuracy, the inability to understand the reasoning behind these predictions could be a potential stumbling block in the broader acceptance and application of such models in clinical settings (31).

The concern surrounding the 'black box' nature of AI models, first delineated by Holzinger et al. in 2017, is a palpable barrier to their extensive adoption, particularly in the medical community (32) and end-to-end models.

A black box model is defined by its extreme mathematical complexity, which obscures the very nature of its internal decision-making mechanisms. In essence, a black box AI model takes an input, processes it through a complex web of computations, and outputs a result, all without offering clear insight into how that result was reached. This absence of transparency and interpretability can be disturbing for professionals in any field. Still, in medicine, where decisions directly impact human lives and can have profound consequences, the lack of understanding of how decisions are reached is especially concerning.

A physician's trust in a tool or a procedure often arises from a clear understanding of its mechanisms, and it is this clarity that AI models often lack (33). The integrity of the patient-doctor relationship and the implicit trust placed in a physician's decision-making are not to be taken lightly. These factors are fundamentally based on the understanding of the methods, procedures, and decisions made. When AI is introduced without proper interpretability, it jeopardizes this trust and is likely to be met with resistance.

Moreover, the opacity of AI decision-making raises ethical and legal questions. The moral responsibility of a decision in medicine usually lies with the clinician making the decision. However, if an AI tool is involved, and an error occurs, it may be difficult to attribute responsibility (34). Wachter et al. (35) pointed out the challenges in this regard, particularly because a clear comprehension of how the AI arrived at its decision is often difficult to trace.

Explainable AI emerges as a promising solution to these concerns. The creation of AI models that maintain high performance while also offering transparency in their workings is an hot field of research (36). These models strive to strike a balance between the accuracy of a deep learning model and the transparency of a simpler model.

In theory, the development of explainable AI seems straightforward, but in practice, it is a complex undertaking, fraught with challenges. One such challenge is maintaining the balance between model complexity and interpretability. Simpler models are typically more interpretable, but they often compromise on accuracy. On the other hand, more complex models, while highly accurate, sacrifice transparency and interpretability (37).

Research into explainable AI is a pressing subject, given the rising usage of AI in various fields, particularly in healthcare. Designing these models is not just a scientific challenge but also an issue of trust, ethics, and legal responsibility. From a scientific perspective, it represents one of the frontiers of AI research. From an ethical perspective, it poses questions about responsibility, transparency, and trust. From a legal standpoint, it begs the question of culpability when errors occur (35). From the government certification agencies for medical products, there is a growing requirement for a comprehensive examination of the interpretability of AI models used in medicine, despite it being a complex challenge that depends on each type and architecture of neural network (usually preserved as industrial secret).

The integration of AI into clinical practice must grapple with the ongoing issue of the black box problem. Physicians' trust, ethical responsibility, and legal accountability are vital considerations that must be addressed as we advance further into this technological age. The development of explainable AI offers a potential solution, but substantial challenges must be overcome before we can fully reap the benefits of AI in a responsible, transparent, and trustworthy manner.

The task of handling unstructured medical data

The digital revolution in the medical sector has seen an exponential increase in the generation of computerized medical data. Much of this data, encompassing clinical notes, radiology images, pathology reports, among others, exists in an unstructured format, posing a considerable challenge in leveraging this data for advanced computational applications such as artificial intelligence. As a result, one significant task faced by the medical community is the conversion of unstructured data into a form that can be feed into AI algorithms (19). It is worth noting that this process is not trivial; it involves labor-intensive and time-consuming operations that require sophisticated methodologies and tools.

The complexity of the process arises from the arbitrary and diverse nature of unstructured medical data, which is typically characterized by a lack of predefined format, making it difficult to classify, interpret, or utilize in AI models (38). It also contains a wealth of information critical to patient care and clinical decision making, including details about a patient's history, condition, treatment options, and prognosis. Consequently, the conversion process must not only be meticulous but also comprehensive, ensuring that the rich information content is preserved while being made accessible to AI models.

Nevertheless, the benefits of achieving this task are significant. The ability of AI models to handle and interpret unstructured data could significantly increase the utilization of medical data, thereby augmenting the quality of AI-assisted clinical decision-making. For instance, in a study by Rajkomar et al. (39), a deep learning model was developed that could make accurate predictions about various patient outcomes, such as length of hospital stay and readmission likelihood, by utilizing electronic health record data, including unstructured data like clinical notes. This example illustrates the potential value of unstructured data in enriching AI models, which in turn can enhance the quality of care delivered to patients.

However, the development of AI models capable of managing unstructured medical data remains a challenging task due to various reasons. For example, the unique characteristics of medical data, including its diversity, sensitivity, custom acronyms, and size, necessitate specialized and advanced techniques for processing and handling it (40). Furthermore, the absence of standardization in the representation of unstructured medical data adds to the complexity of the task. Moreover, ethical and legal considerations surrounding the use of medical data, particularly in the context of AI, present another layer of challenges that need to be addressed.

Overcoming these challenges necessitates a multidisciplinary approach that combines expertise in areas such as data science, machine learning, medical informatics, and healthcare law and ethics. It also requires collaboration between various stakeholders, including clinicians, data scientists, ethicists, and policymakers, to ensure the responsible and effective use of unstructured medical data in AI (41).

Handling unstructured and multimodal medical data is a challenging yet essential task in the field of medical AI. It demands sophisticated methodologies, collaborative efforts, and the addressing of ethical and legal considerations. However, achieving this task could significantly enhance the quality of AI-assisted clinical decision-making.

The development of AI tools that can handle multiple comorbidities

Initial efforts in AI predominantly targeted singular diseases (12). This approach aligns with traditional biomedical research, which generally prioritizes understanding individual diseases in isolation (42). While this strategy is valuable, it fails to account for the intricate relationship between multiple concurrent diseases in a patient. This issue is a stark contrast to real-world clinical practice, where patients often present with multiple concurrent diseases or comorbidities (43). In reality, patients often present with comorbid conditions that can modify disease expression, prognosis, and response to treatment (44). Recognizing and addressing

this discrepancy requires the development of advanced AI models capable of managing this level of complexity.

Moreover, developing AI models capable of handling multiple comorbidities is far from trivial. Comorbidities are not merely a collection of individual diseases but a complex network of interconnected conditions (45). Consequently, AI models must account for the non trivial interconnections among different diseases. Moreover, these models must factor in how the presence of multiple comorbidities might affect a patient's health status, treatment response, and prognosis (46). Consequently, the development of such models involves sophisticated computational methodologies and data management, requiring extensive knowledge in both medical science, software engineering and AI technologies (47).

An important step in this development process is the availability of high-quality, comprehensive patient data (see section 0). The creation of these models depends on access to extensive datasets detailing patients' disease history, including all concurrent conditions and their progression over time. While such data is typically available in electronic health records (EHRs), several barriers exist to its utilization (48). These include issues relating to data privacy and security, data quality and consistency, and the lack of standardized methodologies for extracting meaningful information from EHRs (24).

Despite these challenges, significant progresses have been made in the development of AI models capable of handling multiple comorbidities. For example, a model proposed by Choi et al. utilizes graph-based deep learning to predict future comorbidities in patients (49). This model, known as the Medical RelationNet, uses EHR data to construct a patient-disease-time graph, which it then uses to predict the future onset of comorbid conditions. While this model represents a significant advancement in this field, more work is needed to develop AI models that can not only predict comorbidities but also provide personalized treatment recommendations (see section 0).

Developing AI algorithms that can effectively deal with rare diseases

The capacity of artificial intelligence and machine learning (ML) to manage and to diagnose rare diseases represents a domain still in its nascent stage. The fundamental challenge resides in the scarcity of data pertinent to these conditions. These diseases, while individually infrequent, collectively affect a significant portion of the global population (50).

In the domain of machine learning and Statistics, the "Long Tail" refers to the distribution of classes where a limited number of classes have abundant instances (the "head") and a large number of classes have few instances (the "tail"). In this distribution, rare diseases fall into the "tail" segment, thus posing unique difficulties to the ML algorithm development. Despite the considerable improvements in AI techniques, algorithms are still primarily reliant on large datasets for effective training (51).

The relative paucity of shared public data concerning rare diseases affects the performance of AI models in two primary ways. First, the limited availability of data impacts the model's ability to recognize the distinguishing patterns and features of rare diseases (52). Second, the

lack of variability in the sparse data hinders the generalizability of the model. These two facets form the core obstacles in training AI models to effectively manage rare diseases.

One proposed solution to this problem involves the utilization of transfer learning. Transfer learning enables the adaptation of a pre-trained model on a new task with comparatively fewer data, exploiting the commonalities and differences between the tasks. This method has been successfully applied in several medical imaging contexts (53,54). Nonetheless, it requires a careful design to ensure the similarity between the source and target tasks, which might not always be feasible in the case of rare diseases.

In parallel, data augmentation techniques can be employed to artificially inflate the limited dataset size. Methods such as synthetic minority over-sampling technique (SMOTE) have been employed with encouraging results in other areas of medicine (55). Moreover, advances in synthetic data generation, offer promising directions for addressing data scarcity in rare diseases (56).

Collaboration and data sharing among healthcare institutions and researchers around the globe could markedly enhance the capacity to develop efficient AI models for rare diseases. In an exemplar case, an international collaborative project called 'Genomics England' has resulted in the sequencing of 100,000 genomes from around 85,000 NHS patients, including many with rare diseases, creating a valuable dataset that could be instrumental for the development of certain AI models (57).

Ensuring the continuous learning and adaptation of AI models while maintaining their safety and performance

The advancement and expansion of medical knowledge necessitate a periodic update of the AI models. Notwithstanding the perceived benefits of such updates, they carry potential alterations in model behaviour, thereby eliciting unforeseen consequences (6).

These AI models might play become 7/24h assistants in diagnostics, prognostics, treatment strategies, and managing public health emergencies, thereby emphasizing the need for ensuring safety and efficacy. The premise of AI models' success rests on their ability to learn, adapt, and improve performance continuously over time, which implies training on expansive and diverse datasets (1). The concept of frozen or static models falls short in the medical domain, given the inherent dynamic nature of medical science and the necessity of staying up-to-date with new research, best practices, and clinical guidelines (33).

Integrating new knowledge into AI models necessitates an understanding of the repercussions this might have on their behaviour. These transformations, although intended to enhance the performance and applicability of the model, might bear the potential to sway the model's behaviour, inducing unanticipated outcomes (58). Therefore, any update process needs to be structured and monitored to ensure a balance between the incorporation of new knowledge and the safety and efficacy of the model. The focus, thus, is to create secure environments that enables continuous learning and adaptation without compromising model safety or performance.

Regulating updates to AI models poses a set of formidable challenges (see section 0). The maintenance of an AI model's safety and efficacy is an iterative process, involving a cyclic methodology of update, testing, validation, and deployment. It is necessary to ensure that an update does not lead to "catastrophic forgetting," where the model may lose its ability to perform tasks it was previously trained for. One such method to mitigate this issue is 'elastic weight consolidation,' which protects the parameters important for previously learned tasks during the learning of new ones (59), although it is quite dependent on the underlying Deep Learning architecture. Another approach is the development of automated and continuous monitoring systems to detect and mitigate unexpected behaviour changes in deployed models (60).

However, not all model updates result in significantly altered behaviours. In fact, some updates, such as those involving bug fixes or minor adjustments, may be largely benign and have little to no impact on the safety or performance of the AI system. This highlights the need for a systematic and graded approach to updates, which carefully considers the potential impact of each change and prioritizes thorough testing and validation for more significant updates.

The challenge of balancing updates with safety and efficacy of AI models is another pressing issue. A framework is required that enables the incorporation of novel medical knowledge, supports the ability to adapt and improve, and ensures the safety and performance of the model are upheld. Such a framework will benefit from collaborative efforts from the spheres of medical science, artificial intelligence, and regulations.

Designing user interfaces for AI tools that are intuitive and user-friendly

The employment of artificial intelligence in healthcare is increasing rapidly and is reshaping many aspects of medical practice, from diagnosis and treatment planning to patient management and follow-up (2). This proliferation has engendered an imperative need for effective user interfaces (UI) that enhance rather than obstruct the communication between the human end-users, predominantly healthcare providers, and AI tools. The UI is essentially the point of interaction between the users and the AI tools, and its design determines the degree of utilization and adoption of such systems in the clinical practice (61).

Efficiency, intuitiveness, and user-friendly attributes are often designed carefully in UIs for AI tools (62). Efficiency sums up the need for a swift and precise response, necessitating the interface to possess capabilities for timely data retrieval and presentation, fast data entry, and immediate responses to user commands. An intuitive design allows users to predict the behaviour of the AI tools without requiring extensive training or having to resort to a user manual. User-friendly interfaces, on the other hand, prioritize the ease of use and understandability, making them accessible and comfortable for users with varying levels of technical proficiency.

A judicious integration of these principles into UI design of AI tools could improve the effectiveness and acceptance among healthcare providers. Research conducted by Patel et al. has demonstrated that the appropriate design of UIs for AI tools in healthcare could result in

improved user satisfaction, increased productivity, and more precise medical decision-making (63).

Yet, suboptimal UI design may present considerable challenges, affecting user acceptance and utilization. A poorly designed UI can increase cognitive load, resulting in user frustration and decreased productivity (64). More concerning is the potential for patient harm. For instance, incorrect interpretation or misunderstanding caused by a baroque interface could lead to misdiagnoses, inappropriate treatments, or other detrimental clinical decisions.

As we delve further into the implications of UI design in the context of AI in healthcare, it's valuable to reflect on the example of IBM's Watson for Oncology. As reported in Strickland (65), despite the system's powerful underlying AI technology, physicians were often frustrated by the complex and unintuitive interface, leading to low adoption rates and criticisms of its applicability in real-world practice. This experience underscores the critical role of interface design in AI tool acceptance and effectiveness.

Therefore, the design of UI for AI tools in healthcare should be a meticulous and thoughtful process, requiring a multi-disciplinary approach that includes not only designers and AI specialists but also end-users, the healthcare providers themselves (66). This would ensure that the AI tools are indeed suited to the real-world, high-demand environment of healthcare provision, aligning with the unique requirements and workflows of the sector.

While the potential of AI in healthcare is vast, the success of AI tools will be dependent not just on the sophistication of the underlying algorithms, but also on the effectiveness and usability of the interfaces through which users interact with these systems. Future research should continue to explore the optimal design principles for AI tool interfaces in healthcare, ensuring their alignment with user needs and clinical workflows.

HEALTHCARE AI INTEGRATION AND OPERATIONALIZATION CHALLENGES

The current technological revolution is by no means the first experienced by the medical world. Medicine has been closely tied to disruptive technological changes since its inception (67), as a significant portion of human ingenuity is invested in improving the quality of life for others and, consequently, in combating illness with all the tools at our disposal.

This factor necessitates that the implementation of AI-based solutions must compete and adapt within a framework of previously deployed technologies, which have seldom been designed to be scalable or collaborate with systems of such advanced nature.

The subsequent sections delve into the challenges surrounding these matters, which must evolve concurrently with the adoption of these technologies that offer us so many advantages (3).

The integration of AI into clinical workflow

Artificial intelligence applications in healthcare hold a remarkable potential to transform clinical practice through streamlining workflows, improving diagnostic accuracy, and

enhancing patient care (67). Thus, it is necessary to consider how these systems integrate into existing healthcare practices, how they interact with healthcare information technology (IT) systems, and how user-friendly they are to the clinicians who will be using them in real-time.

In the current landscape, many AI tools have been created as stand-alone systems, posing a significant challenge to their incorporation into the clinical workflow. This separation from established systems can result in additional work for healthcare providers, as these systems often require additional and customized interface and data entry process to interact with. Rather than augmenting the clinician's work, these stand-alone AI systems may disrupt the delivery of patient care by adding another layer of complexity to the provider's tasks. This issue is highlighted in the research by Blease et al., where the authors underline the necessity of integrating AI systems into the existing healthcare IT infrastructure to ensure seamless operation and avoid unnecessary burden on clinicians (68).

Addressing this challenge necessitates the development of AI systems that are not only interoperable with existing healthcare IT systems but also align well with the clinical workflow. This factor involves a full understanding of the needs, preferences, and routines of the healthcare providers who will be using these systems in their practice. The AI tools should be designed to augment the clinician's work rather than replace it, offering assistance in real-time without disrupting the clinical workflow. Integration can be facilitated by creating AI systems that are compatible with existing electronic health records (EHRs) and other healthcare IT systems. Such an approach was presented by Rajkomar et al. where the authors showed how machine learning models can be integrated into EHRs to predict medical events (39).

However, integration and interoperability are not sufficient to ensure the effective use of AI in clinical practice. Another key consideration is the training and preparation of end-users: the clinicians and their assistants (69). Despite the advancement of AI technologies, the proficiency and confidence of clinicians in using these tools remain limited. This limitation can lead to a lack of trust and adoption, inhibiting the full potential of AI in healthcare. As noted by Johnson et al., it is necessary to provide healthcare providers with adequate training to use AI tools effectively(69), including an understanding of their underlying principles, the potential benefits, and the limitations (70).

The technical difficulties of integrating AI with existing health IT systems

The implementation of AI into existing health IT systems poses a significant technical challenge, especially considering that many healthcare organizations continue to use older IT infrastructure, which are not easy to integrate to improve patient monitoring and administrative processes powered by AI-based software (71).

A fundamental issue to address in the integration of AI with current health IT systems is the heterogeneity and fragmentation of these systems. Many hospitals and health institutions operate with a multitude of disparate and often outdated IT systems, not designed for interoperability (1). These systems tend to be siloed and only compatible with same vendor tools, making data extraction, sharing, and utilization for AI applications a complex task (72).

For example, the adoption of the Epic System by Kaiser Permanente, a leading healthcare provider in the United States, highlights the struggle to streamline patient records across different facilities due to the significant variance in data structure and language (see section 0).

Moreover, data quality and consistency present notable hurdles. Deep Learning models rely on large, structured, and high-quality datasets to produce meaningful and accurate results (6). However, in healthcare settings, data are frequently unstructured, heterogeneous, and inconsistent due to variations in input methods and procedures, potentially leading to issues with accuracy and reliability in AI applications (73) (see section 0). Furthermore, the quality of data can be compromised due to errors, omissions, and biases in recording practices, which pose significant challenges to the training of AI models. For instance, a study in the UK demonstrated that inconsistent coding practices in electronic health records led to substantial discrepancies in stroke event recording, an issue that could significantly impact AI models' performance in predicting stroke events (74).

Additionally, the technological readiness and capacity of the existing health IT systems play a crucial role in the successful integration of AI. These older systems often lack the required computational power and capabilities for advanced AI applications (1). Consequently, the process may necessitate substantial upgrades or complete renovations of the existing infrastructure, which could entail significant financial investment and potential workflow disruptions (47).

Furthermore, the complexities related to data privacy, security, and regulatory compliance cannot be understated. Health data are sensitive, and their management involves strict regulatory frameworks to ensure patient privacy and data security (75). The integration of AI solutions into health IT systems necessitates robust mechanisms to ensure data are handled, processed, and stored in ways that comply with laws such as the Health Insurance Portability and Accountability Act in the United States or the General Data Protection Regulation in the European Union.

AI validation and regulation

The introduction of artificial intelligence in healthcare has opened new possibilities for diagnosis, prognosis, and management of disease conditions. Its effective and safe application in real-world clinical settings necessitates a thorough validation process that recognizes and addresses the innate complexities and variations in clinical practices, patient populations, and disease patterns. These elements have been identified to significantly impact the effectiveness of AI in actual healthcare environments, leading to its performance that is often not as promising as it is in controlled research scenarios (76).

The heterogeneity inherent in real-world patient populations and clinical practices poses a unique challenge to AI validation. Disease manifestation and patient response can vary significantly due to a myriad of factors such as age, gender, ethnicity, comorbidities, and socioeconomic status, among others (77). This considerable variation requires AI systems to be adaptable and generalizable to deliver precise and effective care. Similarly, the shifting

patterns of diseases over time, influenced by factors such as lifestyle changes, genetic evolution, and environmental changes, necessitate AI's adaptability to continue being effective (78).

To achieve this level of adaptability and generalizability, rigorous large-scale, multicenter clinical trials are recommended as they expose AI systems to a wide range of clinical and demographic variations. These trials serve as a crucial validation process that evaluates not only AI's accuracy but also its safety, effectiveness, and ability to generalize its learning across diverse scenarios (79). However, conducting these trials comes with its own set of challenges. Logistical difficulties, such as data sharing issues, patient privacy concerns, and difficulty in standardizing trial protocols across different centers are some of the many hurdles. Furthermore, the financial burden associated with these large-scale trials can be substantial, often proving prohibitive, particularly for smaller companies and institutions (80).

The second layer of complexities in validating AI for healthcare arises from the current regulatory frameworks. AI, in its essence, is a continuously learning and adapting system. This characteristic, while being one of its strengths, also presents unique regulatory challenges (see section 0). The Food and Drug Administration (FDA) and similar regulatory bodies have long-established protocols for approving medical devices and interventions. However, these traditional protocols are ill-equipped to handle the dynamic nature of AI systems. The current regulations demand a static validation process that is incompatible with the continuous learning and adaptation of AI (81).

To address these challenges, there is an immediate necessity for innovative validation strategies and updated regulatory norms. The validation strategies need to take into consideration the heterogeneity of real-world healthcare settings and the dynamic nature of AI, designing comprehensive protocols that allow rigorous testing of these systems. Updated regulatory norms, on the other hand, should accommodate the evolving nature of AI systems while ensuring patient safety and efficacy of AI interventions (82).

However, the development and implementation of such strategies and norms will require concerted efforts from all stakeholders, including researchers, clinicians, regulators, and patients. Moreover, a balance needs to be struck between encouraging innovation and maintaining stringent safety and efficacy standards. It is, therefore, a subject of ongoing research and discussion.

Managing the expectations of healthcare providers and patients regarding AI

An overestimation of AI's capabilities or an underestimation of its limitations may lead to disillusionment among healthcare providers and patients, potentially inhibiting the acceptance and integration of AI in healthcare settings.

Understanding the transformative power of AI in healthcare requires a nuanced appreciation of its capabilities and limitations. AI tools, such as machine learning algorithms, can learn from and make predictions based on training data, thereby enhancing diagnostic accuracy (12). However, they are dependent on the quality and quantity of data they are trained on, and

they require continual refinement to maintain their predictive accuracy (7). These tools do not replace healthcare providers; rather, they augment their ability to make informed decisions about patient care.

Contrary to the notion of AI as a universal solution to healthcare's problems, its application is often context-specific. For instance, AI tools that are effective in tertiary care settings may not be equally effective in primary care or community healthcare settings due to differences in the nature and volume of data, technological infrastructure, and the level of training of healthcare providers (83).

Moreover, the ethical implications of using AI in healthcare should not be overlooked. Issues related to data privacy, algorithmic bias, and the transparency of AI decisions are major concerns that need to be addressed (34). In addition, the integration of AI into healthcare systems may have implications for the patient-provider relationship, potentially disrupting traditional models of care.

Managing expectations of AI in healthcare, therefore, is a delicate balancing act. It necessitates an open, honest, and ongoing dialogue among stakeholders, including healthcare providers, patients, policymakers, AI developers, and researchers. This dialogue should foster an understanding of AI's capabilities and limitations, and the ways in which AI can be responsibly integrated into healthcare practice.

The role of professional bodies, such as the American Medical Association and the British Medical Association, is pivotal in shaping this dialogue. Through their policy statements and guidelines, they can help define the role of AI in healthcare, provide recommendations for its ethical use, and promote education and training for healthcare providers.

Patients, too, have an essential role to play in this dialogue. Patient advocacy groups can empower patients to understand and engage with AI technologies, making them active participants in their care.

The application of AI in healthcare is not an end in itself, but a means to an end. Its ultimate goal should be to improve healthcare outcomes and enhance patient well-being. Any hype surrounding AI should not distract from this goal. A sober appraisal of AI, based on rigorous scientific evidence and thoughtful ethical deliberation, is necessary to realize its potential and avoid pitfalls.

The need for robust cybersecurity measures for AI systems in healthcare

As AI technological advancements continue to permeate the healthcare industry, the risks associated with cybersecurity vulnerabilities concurrently escalate, underscoring the necessity for robust protective measures.

In recent years, the healthcare sector has been increasingly susceptible to a spectrum of cyber threats (84). Among the most prominent concerns are data breaches that could compromise sensitive patient information. The sheer volume of data that healthcare systems process, coupled with its intrinsic sensitivity, makes it an attractive target for cybercriminal activities.

For example, in 2015, Anthem, one of the largest health insurance companies in the United States, experienced a cyberattack that led to the exposure of nearly 78.8 million records containing personal patient information (85,86). Another example is the WannaCry ransom ware attack that occurred on May 12, 2017, impacted 230,000 systems across more than 150 countries, including the UK's National Health Service (NHS) (87). Consequently, from May 13 to 16, 2017, five NHS Trusts were compelled to redirect Accident and Emergency patients to unaffected Trusts, and several Trusts encountered difficulties with their CT and MRI imaging systems. This disruption led to the cancellation of nearly 20,000 appointments or surgeries and incurred a cost of nearly £92 million for the NHS (88). Not only did these breaches result in a significant financial impact, but it also highlighted the potential for severe harm to patient trust in healthcare systems.

Beyond data breaches, there lies an arguably more sinister threat in the form of tampering with AI algorithms. The complexity and opaque nature of some AI systems can render them susceptible to adversarial attacks. Adversarial machine learning, a field that investigates how AI systems can be fooled or manipulated, has documented a variety of potential attack vectors (89). One of the most worrisome is the "poisoning" of machine learning models, wherein attackers insert misleading data into the training phase, leading the model to produce incorrect outputs. In a healthcare setting, such manipulation could lead to incorrect diagnoses, flawed treatment recommendations, and even directly endanger patient safety (90).

Given the severity of these threats, the necessity of robust cybersecurity measures in healthcare AI systems cannot be overstated. It is not sufficient to treat cybersecurity as an ancillary concern; rather, it must be integrated as a core component of the design, implementation, and operation of healthcare AI systems. Such measures may encompass a variety of strategies, from hardened system security and encryption practices to intrusion detection and response systems (2).

Moreover, there is a compelling need for a collaborative approach to cybersecurity in healthcare AI. A multi-stakeholder model involving healthcare providers, AI developers, regulatory bodies, and even patients themselves can enhance shared understanding, establish best practices, and facilitate rapid response to new threats (91). Additionally, international cooperation is vital, given the global nature of cyber threats and the international reach of many healthcare and technology companies.

The importance of obtaining sufficient investment for AI research and implementation

It is necessary to underscore the exigency of securing adequate financial resources for the continuation and expansion of research and implementation in artificial intelligence within the healthcare sector. The current state of AI technology, though promising, remains in its infancy and demands significant funding for further research, rigorous validation, and seamless integration into healthcare systems (2).

There is an expanding body of literature that recognizes the enormous potential of AI to revolutionize healthcare, offering transformative solutions for patient care, disease prevention, diagnosis, and treatment (1). For instance, studies have shown that AI can assist clinicians in

accurately diagnosing diseases, such as cancer, by analyzing medical images and detecting anomalies that might be missed by the human eye (12,92). Despite these breakthroughs, the advancement of AI in healthcare is presently stymied by multiple barriers, not least of which is the lack of sufficient funding.

Securing adequate funding for AI research and implementation in healthcare, however, is a complex endeavour. The investment managers have to deal with competing priorities vie for finite resources (93). The significance of this challenge cannot be overstated, given the myriad issues that persist in healthcare, such as chronic disease management, elderly care, and health inequality, all of which necessitate immediate and tangible solutions. In such a context, prioritizing funding for a still emerging technology can be a contentious issue.

A particular concern is the validation of AI technology. Unlike traditional pharmaceutical or biomedical research, AI applications require unique validation processes, often involving large and diverse datasets (94). Furthermore, AI applications need to be validated in a real-world clinical setting, a process that is both time-consuming and costly. The financial burden of validation hence poses a significant barrier to the deployment and adoption of AI in healthcare.

Additionally, the integration of AI into existing healthcare systems is another substantial financial endeavor. Even with promising AI applications, the transition from development to integration is fraught with obstacles. For instance, the deployment of AI necessitates changes in the existing workflow, training for healthcare professionals, and infrastructure upgrades, all of which are costly endeavors (95).

To ensure that the potential benefits of AI in healthcare are realized, adequate investment must be secured. However, this is not merely a question of allocating more funds. Rather, it necessitates a multi-faceted approach that includes policy changes, fostering collaborations between public and private entities, and developing novel funding models that can sustain the growth and adoption of AI in healthcare. The precise direction and shape these efforts will take remains to be seen, but it seems evident that securing the financial resources necessary for AI research and integration requires serious consideration.

Patient-Centric AI Design

The ascent of artificial intelligence into the healthcare domain has inspired fervent discussions regarding its potential advantages and challenges. Among the latter, a subtle yet vital issue arises: the tension between AI's innate drive to generalize and the clinical imperative to individualize. As the integration of AI tools becomes more prevalent in healthcare, striking the right balance between these contrasting tendencies becomes more important. Consequently, patient-centered AI design emerges as a focal area of interest, intertwining technology's capability with medicine's principles.

Traditionally, medicine has flourished on the philosophy of patient-centricity. When a clinician engages with a patient, they aren't just observing symptoms; they're reading a narrative. One shaped by the patient's genetics, environment, history, and lifestyle. This

principle, rooted in the Hippocratic oath, is what has shaped medical decisions, where emphasis is not solely on objective signs but also on the patient's subjective experience (96). With AI's foray into this physician-patient space, the objective may overshadow the subjective, necessitating a design framework that equally respects both.

AI thrives on patterns discernible from large-scale datasets. In this context, these patterns allow for predictions, assessments, and interventions. Yet, human biology and experience, by their nature, do not always conform to discernible patterns. Herein lies the challenge: the granularity of individual experience may be lost in the vastness of data (34).

Moreover, there's the issue of representation. If AI is to be truly patient-centric, it must be trained on diverse datasets, ensuring that every patient demographic is adequately represented, thereby preventing potential biases and misrepresentations (77).

Building a bridge between AI's pattern-seeking essence and the particulars of individual patient stories requires deliberate action. Multi-modal data integration, which brings together diverse sources of patient data, stands as a promising avenue. By considering genetic, physiological, psychosocial, and other variables, AI can foster a richer, more nuanced understanding of individual health profiles.

Ethics remains at the core of this integration. Beyond the crucial matter of data privacy, there is an inherent duty to ensure AI tools are developed and utilized with transparency and respect for patient autonomy (82).

AI Governance and Oversight

While there is general consensus on AI's transformative potential, the medical community remains split on its trajectory, especially concerning the necessary governance and supervising structures.

One of the more remarkable concerns in the introduction of AI into healthcare revolves around the notion of trust. For healthcare professionals to adopt and, more importantly, rely on AI-driven systems, they need to trust the decisions and recommendations these tools make. But trust in AI isn't binary; it requires an understanding of the system's mechanisms, or at the very least, its logic. The non-transparent nature of certain advanced algorithms (see section 0), which make them almost inscrutable, poses a challenge in building this trust (97). Hence, it becomes vital for any governance framework to emphasize interpretability and transparency as core principles for AI tools in healthcare.

Another governance challenge emerges from the data upon which AI systems are trained. Medical data, inherently complex and multifaceted, can sometimes be unrepresentative or contain implicit biases. Systems trained on such data can inadvertently perpetuate or even exaggerate these biases, leading to imprecise or biased clinical recommendations (77). Thus, an integral part of AI governance must involve rigorous data validation and constant oversight to ensure data quality and representativeness.

The AI-governance nexus also intersects with regulatory standards that already exist in healthcare. How should regulatory bodies approach AI? Is there a need for new structures, or can AI be accommodated within the current regulatory frameworks? The dynamic and evolving nature of AI, wherein systems continuously learn and adapt, poses a unique challenge. Unlike static medical devices or interventions, AI-driven systems can evolve post-deployment, necessitating periodic reassessment and validation (98).

From an ethical vantage, there are additional layers of complexity. Issues like patient consent, data privacy, and the potential for misuse take center stage in discussions about AI's integration into healthcare (99). AI governance frameworks should be constructed with these ethical considerations at their core, perhaps even mandating ethics committees specifically for AI-related interventions in medical settings.

The marriage of AI and healthcare, while promising, is rife with challenges that demand well-thought-out governance and oversight. Constructing such frameworks requires a multidisciplinary approach, combining technological expertise with clinical, ethical, and regulatory insights. Only with such comprehensive governance can we ensure that the transformative potential of AI in healthcare is realized responsibly and safely.

HEALTHCARE AI ETHICAL, SOCIAL, AND EQUITY CHALLENGES

The adoption of artificial intelligence in healthcare marks a significant transition, affecting patient care strategies, disease prediction methods, and the direction of medical research (2). As AI technologies become more commonplace in healthcare settings, a range of ethical, social, and equity considerations emerges, warranting thoughtful analysis. While the advantages of AI—such as enhancing diagnostic accuracy, streamlining clinical processes, and tailoring patient care—are evident, there are concurrent concerns about patient data protection, potential biases in AI systems, and equitable access to these technologies.

The following sections delve into the challenges revolving around these matters. While they possess a more human dimension, they cannot be detached from the challenges of a more technological nature addressed in the preceding sections.

Data privacy and patients' data anonymization

Medical practices are about to experience profound shifts with the emergence of artificial intelligence, particularly in predictive modelling derived from patient health records.. These records, however, are typically replete with highly sensitive personal data, presenting an intricate quandary of data privacy and protection (100). The proliferation of data breaches in recent years has underscored the urgent necessity of safeguarding such data. In an age where privacy has come to the fore as a global concern, AI medical practitioners face the task of navigating a delicate equilibrium. On the one hand, they must advance AI-driven healthcare innovations. On the other, they must uphold patients' rights and confidentiality by ensuring data protection (101).

The challenge is further amplified by the introduction of robust data protection legislation like the European General Data Protection Regulation (GDPR), which imposes strict constraints

on data usage (102). GDPR and analogous legislation enacted worldwide delineate a series of stringent conditions for the acquisition, storage, processing, and disclosure of personal data, thus establishing an additional regulatory obstacle for AI applications in healthcare. Navigating the legal landscape, AI experts must formulate a balanced strategy that respects data protection mandates while also fostering the progression of AI within healthcare.

The dichotomy between safeguarding data privacy and fostering AI's progress in healthcare can be traversed through strategies that employ data anonymization and de-identification. Anonymization, as defined by the GDPR, is the irreversible process of transforming personal data such that the data subject cannot be identified. This practice, when employed judiciously, can act as a potent instrument for achieving a balanced approach. Data anonymization techniques, such as k-anonymity, l-diversity, and t-closeness, aim to mitigate the risk of re-identification while maintaining the utility of the dataset for research and AI-based analysis (103).

The potential of these techniques is exhibited in a study by El Emam et al., wherein a de-identified dataset was successfully utilized for a drug safety surveillance project without breaching patient privacy (104). While the example demonstrates the feasibility of anonymization and de-identification, it also emphasizes the care that needs to be taken to ensure the techniques are applied rigorously and correctly. Inaccurate or inappropriate de-identification can result in residual risks of re-identification, thus compromising data security (105).

Although there's no one-size-fits-all solution to the complex puzzle of data privacy in AI-driven healthcare modeling, the prudent application of anonymization and de-identification methods holds promise. AI practitioners must strive to incorporate these methods into their data protection strategies to uphold patient privacy, abide by legal norms, and sustain the progress of AI in healthcare.

The potential widening of health disparities

Without a careful implementation, AI systems may inadvertently magnify health disparities.Health disparities can be thought of as the unequal distribution of health resources or outcomes across different groups, typically associated with socioeconomic status, race, ethnicity, or geographic location. It has long been documented in the literature that certain communities experience disproportionately negative health outcomes due to such disparities (106). If AI-based tools, which have the potential to be a great equalizer, are trained primarily on data from specific demographic or socio-economic groups, they may not function as effectively when applied to other populations.

The issue at hand is that medical AI systems, like all machine learning algorithms, are only as good as the data on which they are trained. The machine learning models used in AI systems do not generate knowledge or understanding independently; they learn patterns from the input data they are given (107). If the data used to train these models are not representative of the diversity of populations that will use the healthcare services, then the AI system may generate biased results, which can lead to suboptimal care for underrepresented groups.

A notable example of this issue can be seen in a study by Obermeyer et al. (7), where an AI system used to identify and prioritize patients for high-risk care management programs was found to be biased against African Americans. Despite having similar health needs as white patients, African Americans were less likely to be identified as high-risk by the AI system. The source of the bias was traced back to the algorithm's training data, which used healthcare costs as a proxy for health needs. Given that African Americans tend to spend less on healthcare due to existing disparities, the AI system was inadvertently perpetuating these disparities.

The potential exacerbation of health disparities by AI systems presents a significant challenge to healthcare providers, researchers, and policymakers. However, it also presents an opportunity to rethink how we design and implement AI systems in healthcare. Greater diversity in data collection and more inclusive algorithmic design can ensure that AI tools provide equitable health outcomes. By incorporating data from a wider range of demographic and socio-economic groups, we can create AI models that generalize better across populations. This requires a coordinated effort from all stakeholders, including healthcare providers, AI developers, patients, and regulatory bodies.

AI systems should be developed and deployed with clear, understandable explanations of how they operate and make decisions (see section 0). This will empower patients and healthcare providers to make informed decisions, potentially alleviating some of the distrust that may arise from opaque AI systems.

While AI has the potential to democratize healthcare, it also has the potential to widen existing health disparities if not implemented thoughtfully. The key to ensuring equity in AI applications lies in diverse data collection, inclusive algorithm design, and transparent implementation practices. These efforts can help mitigate potential bias in AI systems and contribute to more equitable health outcomes.

Maintaining a humanistic approach to healthcare in an AI-driven environment

The future ubiquity of AI in the healthcare sector has raised concerns about the maintenance of a humanistic approach to patient care. This approach is fundamental in the medical practice, it emphasizes the importance of empathy, compassion, and interpersonal relationships, qualities that are not readily reproducible by AI (95).

One aspect worth discussing is the preservation of empathy in an AI-mediated healthcare context. Empathy is a fundamental aspect of the physician-patient relationship, it allows healthcare providers to understand and resonate with patients' emotional states, leading to improved therapeutic outcomes (108). The reliance on AI tools, while expediting healthcare delivery, could potentially depersonalize patient care, creating an environment that might feel cold and devoid of human warmth and understanding. However, to reconcile AI integration with empathetic care, it is important to recognize the distinct roles of AI and healthcare professionals. AI excels in standardizing and streamlining tasks, analyzing vast amounts of data, and delivering evidence-based predictions, whereas healthcare professionals bring a nuanced understanding of human emotions, patient narratives, and holistic care (109).

In addition to empathy, compassion is an integral part of the therapeutic alliance between physicians and patients. The experience of compassion, not just as a sentiment but as a committed action to relieve suffering, underlies every clinical encounter (110). As AI tools become more embedded within clinical practice, it is essential to ensure that they are used as instruments that aid compassionate care, rather than as replacements for human providers. For instance, AI could be leveraged to handle administrative burdens, freeing clinicians to spend more quality time with patients, thereby fostering a deeper connection (111).

Moreover, the preservation of interpersonal relationships in an increasingly digital healthcare ecosystem cannot be forgotten. The art of medicine relies significantly on the physician-patient relationship, a delicate dynamic built upon mutual trust and respect. This relationship is decisive for eliciting patient histories, making accurate diagnoses, and implementing effective treatment strategies (112). In the midst of the rapid digitalization of healthcare, there is a risk of this relationship becoming more transactional and less personal. Therefore, the challenge lies in the strategic implementation of AI to supplement rather than supplant these human connections (113).

The emergence of AI as a driving force in healthcare necessitates a conscientious appraisal of the roles that empathy, compassion, and the physician-patient relationship play in healthcare delivery. As we integrate AI into the healthcare scene, it should be regarded as a tool to enhance, not replace, the humanistic qualities that are central to the practice of medicine(114-115). It is through this careful and mindful integration of AI that we can uphold the humanistic values that form the heart of healthcare, despite the changing landscape.

Achieving broad-based consensus on the ethical use of AI in healthcare

As artificial intelligence becomes an integral part of modern healthcare, it gives rise to ethical challenges related to data privacy, informed consent, accountability, and equitable access, necessitating broad-based consensus from all stakeholders (82).

The integration of artificial intelligence in healthcare necessitates stringent measures to safeguard patient data privacy. It is essential to consider that the use of large data sets, a key element in training AI models, could potentially compromise patient anonymity if not appropriately de-identified and secured (34). Despite the existence of data protection regulations like the General Data Protection Regulation (GDPR) in the EU and the Health Insurance Portability and Accountability Act (HIPAA) in the US, the question persists as to whether these are adequate to address the unique privacy concerns posed by AI in healthcare (35). Therefore, strategies to ensure the ethical use of patient data should be developed, taking into account not only the de-identification and secure storage of data but also the ethical considerations surrounding its use.

Concurrently, the matter of informed consent for AI-assisted care is matter of great importance. The integration of AI into healthcare necessitates a re-evaluation of the traditional model of informed consent. Ordinarily, informed consent involves explaining the risks and benefits of a proposed intervention to a patient, but AI's complexity and current inherent unpredictability could challenge this model (116). Given that AI algorithms often operate as

'black boxes' with decision-making processes that are opaque even to the developers, it can be challenging for patients to fully understand the risks and benefits of AI-assisted care (81). This issue underscores the necessity for redefining informed consent in the era of AI, ensuring it encompasses the unique challenges posed by these technologies.

Further, accountability in the case of AI errors needs to be established. An error made by an AI system can lead to misdiagnosis or mistreatment, posing serious risks to patients. It can be challenging to determine responsibility in such cases, given that AI's decision-making process can be complex and opaque. Current malpractice laws and regulations may not be sufficient to address this new paradigm, and therefore novel legal frameworks are necessary to identify the responsible parties when AI causes harm (117).

Lastly, the potential benefits of AI in healthcare should be equitably distributed. Access to AI technologies in healthcare is likely to be initially concentrated in affluent urban areas, possibly exacerbating existing health disparities (118). For instance, rural areas and low-income regions, both within and between countries, may not have the same access to AI technologies, potentially leaving these populations at a disadvantage (119,120). Hence, it is critical to ensure that the benefits of AI in healthcare are widely available and that mechanisms are in place to avoid exacerbating health disparities.

While AI presents numerous opportunities for advancing healthcare, it also raises significant ethical issues that need to be addressed. Broad-based consensus among all stakeholders is needed to ensure the ethical use of AI in healthcare, considering the unique challenges posed by data privacy, informed consent, accountability, and equitable access.

Managing the potential workforce implications of AI

Artificial Intelligence integration has raised concerns about potential workforce implications, necessitating a thorough understanding and careful management of these changes to uphold high-quality patient care.

One of the primary aspects to consider is job displacement or redundancy due to AI. AI has been proclaimed for its ability to automate routine and tedious tasks, which in a healthcare setting range from administrative responsibilities to patient triage (68). This enhanced efficiency raises the question of whether some roles currently fulfilled by humans may become unnecessary. Previous studies have suggested that while AI has the potential to automate certain tasks, the scope for complete replacement of healthcare professionals remains limited (107). The integration of AI, therefore, does not equate to total job displacement but a reconfiguration of roles, necessitating a nuanced understanding of its implications.

The advent of AI has generated a shift in the roles and responsibilities of healthcare professionals by making them more time-efficient. It is a shift towards tasks that necessitate human judgment, empathy, and complex decision-making, rather than tasks that are routinized or systematic in nature. The British Medical Journal's study on the integration of AI in healthcare (1) suggests that clinicians will increase their function as data interpreters, as

AI algorithms process and provide substantial medical data. This evolving role will require that healthcare professionals need to be competent in understanding, interpreting, and applying AI-generated data in their practice.

In managing this transition, it will be necessary to offer training and support to the existing workforce. A study conducted by the National Academy of Medicine (121) suggested the need for ongoing education and training programs that enable healthcare professionals to understand the potential and limitations of AI and to efficiently apply it in clinical practice. There is also an emerging need for interdisciplinary collaboration, particularly with data scientists and technologists, to provide suitable support for AI in healthcare.

Furthermore, AI's integration into healthcare prompts a reevaluation of ethical considerations, particularly regarding patient care and data privacy. An article published in the Lancet (82) proposes that healthcare institutions should uphold transparency in AI application, providing patients with a clear understanding of how their health data is utilized and the role of AI in their care. Ethical principles, such as autonomy, beneficence, and justice, must not be overshadowed by the technological advancement brought about by AI.

The integration of AI into the healthcare workforce poses both opportunities and challenges. A careful approach is required to manage these workforce changes, emphasizing training, interdisciplinary collaboration, and ethical considerations (122). Doing so will ensure that while the healthcare sector leverages the benefits of AI, it maintains the central principle of patient care.

Impact and long-term results assessment of AI medical applications

As artificial intelligence-based solutions become established in the services of various medical specialties, and as solutions that interoperate with each other begin to emerge, the comprehensive care of the patient will be enhanced in the long term.

Firstly, the introduction of AI into healthcare will led to an enhanced quality of care. Machine learning algorithms are being employed in disease diagnosis, where they process and analyze large volumes of data and identify patterns that might elude the human eye. For instance, an AI algorithm has been developed that can detect malignant melanomas with a precision equal to, if not surpassing, that of dermatologists (12). However, it is essential to consider the limitations and biases inherent in AI algorithms. The training data for these algorithms can often be skewed towards certain demographics, thereby affecting the generalizability of results (123).

Further, the adoption of AI has the potential to influence patient outcomes positively. A salient example is one of the Google's DeepMind projects, which developed an AI system that can predict acute kidney injury up to 48 hours before it occurs, potentially giving doctors a significant lead time to intervene (124). However, this presupposes seamless integration with existing healthcare systems and workflows, which is often not the case (see sections 0 and 0).

AI-driven systems, through machine learning algorithms and predictive analytics, offer potential to optimize inventory levels, reduce waste, and streamline procurement processes. A

study by Rajkomar et al. highlighted the ability of deep learning algorithms to predict patient admissions, which can be extrapolated to foresee material and equipment usage patterns, thus aiding in more precise resource allocation (6). A study by Jha and Topol discussed how AI could automate routine tasks, thereby freeing up time for physicians to focus on complex tasks and direct patient care (125). Future artificial intelligence systems will have the capability to detect and alert users when instruments or other devices are not in optimal conditions for their use, thereby promoting proactive maintenance and extending their operational lifespan (126). Nonetheless, the risk of job displacement due to AI cannot be discounted and merits thorough evaluation. As the integration of AI into hospital resource management continues, stakeholders should critically assess the effectiveness and ethical considerations of such applications, ensuring that benefits do not compromise patient safety and care quality.

Biases in AI algorithms, issues in AI implementation, and concerns about job displacement warrant rigorous and ongoing scrutiny. Hence, the integration of AI into healthcare requires a delicate balance, wherein the benefits are maximized, and the drawbacks are mitigated.

Intellectual property and collaboration challenges in medical AI applications

As AI becomes increasingly central to healthcare, the strategies and legal frameworks surrounding intellectual property (IP) rights are key to mediating successful collaboration in this area.

One of the most universal issues regarding IP in medical AI applications pertains to the ownership of algorithms. AI models are generally built on vast datasets to predict health outcomes or suggest potential treatments, among other applications (7). In many cases, the development of these models is carried out by multiple stakeholders—ranging from academic institutions and hospitals to private corporations—which raises complex questions about the ownership of the final product (127).

The complex nature of IP rights in this scenario often leads to protracted disputes over the ownership of algorithms, impeding the sharing of knowledge and slowing down the development of beneficial AI solutions. However, institutions that attempt to bypass these issues by keeping their algorithms entirely private(as industrial secret) face a different set of challenges. Concealing AI models can impede their full validation and hinder the broader scientific community from verifying their accuracy and safety (128).

Data rights also play a significant role in the IP landscape. Many AI models require vast amounts of patient data, and while anonymized datasets can help protect patient privacy, they also introduce other complexities (129). For instance, there are ongoing debates about whether or not these anonymized datasets can be considered a form of IP. Additionally, the sensitive nature of this data necessitates stringent security measures and carefully negotiated data sharing agreements between institutions (130).

While the landscape is fraught with challenges, several strategies have been proposed to help mediate these IP and collaboration hurdles. A potential solution is to establish a more

transparent and standardized framework for the ownership and sharing of AI models and datasets. This could involve measures such as mutually agreed contracts and licensing agreements that define clear parameters for ownership, access, and revenue sharing between collaborating institutions. This approach can help establish a more level playing field and encourage collaboration by reducing the risk of disputes.

Despite these potential solutions, it is important to acknowledge that the landscape of IP and collaboration in medical AI applications is complex and constantly evolving. Therefore, there is an ongoing need for discussion and adaptation to address these challenges and ensure the continued growth and success of AI in medicine.

Global applicability of AI

The global applicability of AI models presents considerable challenges, primarily due to differences in demographics, disease patterns, healthcare practices, and data standards across various countries and healthcare systems.

As indicated along the article, Deep Learning models, by their very nature, operate based on the premise of learning from large amounts of training data. These models make predictions or decisions based on patterns observed in the provided data sets. Consequently, if an AI model is trained on data from a particular demographic or healthcare system, its efficacy may diminish significantly when applied to a different demographic or healthcare system (77). This phenomenon has its roots in the inherent biases of the training data, which may not encompass the variability and diversity present in the global population (7).

Data standards also play a substantial role in the global applicability of AI. Various healthcare systems have different standards and protocols for recording and managing healthcare data (see section 0). The disparities in these standards can lead to inconsistencies in the performance of AI models when applied to different healthcare systems. For instance, the usage of electronic health records (EHR) varies greatly worldwide, affecting the quality and compatibility of data used in AI model training (131).

The challenge, therefore, lies in developing universally applicable AI models or in adapting existing models to different settings. However, achieving this goal is not a straightforward task. An attractive strategy to mitigate this problem is the use of federated learning techniques, where AI models are trained across multiple decentralized devices or servers holding local data samples. This allows the AI model to learn from a diverse array of data sources while addressing privacy concerns associated with data centralization (132,133). Additionally, it is important to ensure that the data used for model training represent a wide demographic range and disease patterns. The inclusion of diverse and representative data aids in overcoming biases and improves the robustness of the models.

However, even as we strive for universality, it must be recognized that adaptations are sometimes necessary, and one-size-fits-all solutions may not be applicable in all contexts. In these instances, transfer learning can be applied, a machine learning method that leverages the knowledge gained from one problem to solve a different, yet related, problem (134). It allows

an AI model trained on a specific setting to be fine-tuned for a different population target, thereby ensuring the wider applicability of AI in global healthcare.

The governmental agencies of each region are making a special effort to ensure that AI-based medical products yield favourable outcomes across the population cohorts of their respective countries. Thus, this challenge is closely intertwined with many of the previously outlined challenges, as model explainability, data quality and traceability, and secure integration into hospital systems' infrastructure are essential in attaining this objective.

CONCLUSIONS

Throughout this extensive review article, we have examined the 24 primary challenges confronting the actual deployment of AI-based healthcare applications. We have strived to provide a rigorous perspective, accompanied by examples of published cases to illustrate each of these challenges.

None of the challenges holds greater importance than the others. In fact, all of them are intricately interconnected (which is why the descriptions of some allude to the others). Thus, a comprehensive approach is imperative for the future adoption of such technology in a domain as sensitive as healthcare.

There is no doubt that we are fortunate to live at the dawn of a bright future, and such applications will enhance physicians' capabilities to be more effective in many ways. The impending revolution will confront each of the current challenges and gradually overcome them. AI-based solutions in the field of medicine will not replace doctors; rather, it will be the physicians who adopt these advancements and tools that will replace those who do not exploit them.

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Chronic Lymphocytic Leukemıa Hospitalized Due To Pleural Effusion - A Case Report

Plevral Efüzyon Nedeniyle Hospitalize Edilen Kronik Lenfositik Lösemi - Olgu Sunumu

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Abstract

Objective: Malignant pleural effusion was detected in 15% of patients who died of malignancy. Chronic lymphocytic leukemia is the most common leukemia in adults. In this case, we aimed to elucidate the importance of pleural biopsy fluid cytology, biochemistry, and imaging.
Case: A 58-year-old male patient with a diagnosis of chronic lymphocytic leukemia was admitted to our institution with complaints of dyspnea and hypoxia. At the time of admission, the patient complained of dyspnea and hypoxia, and evacuatory thoracentesis was performed in order to relieve her symptoms. Fluid biochemistry was exudate, and pathology was benign. Tube thoracostomy was applied upon the recurrence of the fluid. Thorax computerized tomography (CT) revealed no pathology except minimal effusion. Positron emission tomography scans (PET/CT) revealed a slightly increased 18 - Fludeoxyglucose (FDG – 18) uptake in the paramediastinal area. Two closed pleural biopsies were performed, and the result was reported as benign. Upon detection of a 5 cm solid, immobile mass on the right chest wall in control, an incisional biopsy was taken over the lesion. Chemotherapy (CT) and radiotherapy (RT) was initiated. The patient, who was followed up for 3 months for undiagnosed pleural effusion, died from a mass on the chest wall and 2 months after diagnosis of malignant mesothelioma.
Conclusion: In this case, we wanted to emphasize the importance of performing a large-scale open pleural biopsy with absolute vision in recurrent pleural effusions, where fluid cytology, biochemistry, and imaging methods can be misleading and increase the awareness of clinicians.

Keywords: Pleural Effusion, Chronic Lymphocytic Leukemia, Pleural Biopsy.

Özet

Amaç: Malignite nedeniyle ölen hastaların %15'inde malign plevral efüzyon saptanmaktadır. Kronik lenfositik lösemi, yetişkinlerde en sık görülen lösemidir. Bu olguda plevral biyopsi sıvı sitolojisinin, biyokimya ve görüntülemeye karşı önemini aydınlatmayı amaçladık.
Olgu: 58 yaşında kronik lenfositik lösemi tanılı erkek hasta nefes darlığı ve hipoksi şikâyeti ile kliniğimize başvurdu. Hastanın semptomlarını gidermek için boşaltıcı torasentez yapıldı. Sıvı biyokimyası eksudaydı ve patoloji iyi huyluydu. Sıvının tekrarlaması üzerine tüp torakostomi uygulandı. Toraks bilgisayarlı tomografisinde (BT) minimal efüzyon dışında patoloji saptanmadı. Pozitron emisyon tomografi taramaları (PET/CT) paramediastinal bölgede hafifçe artmış 18- Fludeoxyglucose (FDG – 18) alımını ortaya çıkardı. İki adet kapalı plevra biyopsisi yapıldı ve sonuç benign olarak bildirildi. Kontrolde sağ göğüs duvarında 5 cm'lik solid, immobil kitle saptanması üzerine lezyon üzerinden insizyonel biyopsi alındı. Kemoterapi (CT) ve radyoterapi (RT) başlandı. Teşhis konulamamış plevral efüzyon nedeniyle 3 aydır izlenen hasta, malign mezotelyoma tanısı aldıktan 2 ay sonra göğüs duvarındaki kitle nedeniyle kaybedildi.
Sonuç: Bu vakada sıvı sitolojisi, biyokimyası ve görüntüleme yöntemlerinin yanıltıcı olabileceği ve klinisyenlerin farkındalığını artırabileceği tekrarlayan plevral efüzyonlarda mutlak görüş ile geniş çaplı açık plevral biyopsi yapılmasının önemini vurgulamak istedik.

Anahtar Kelimeler: Plevral Efüzyon, Kronik Lenfositik Lösemi, Plevral Biyopsi.

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INTRODUCTION

Malignant pleural effusion (MPE), defined by malignant cells in the pleural fluid or parietal pleura, is seen during many malignancies. Malignant pleural effusion was detected in 15% of patients who died of malignancy. Although it usually develops after the diagnosis of cancer, it can sometimes be the first sign of tumor spread or recurrence. MPE often occurs in advanced patients and is associated with a poor prognosis. Therefore, the main purpose of treatment today is palliation. It has been shown that early mortality is higher in tumors with high malignancy risk, low Karnofsky performance score, low pleural pH, and glucose value. Depending on the stage and type of the underlying malignancy, the median survival after diagnosis ranges from 3 to 12 months (1).

Chronic lymphocytic leukemia (CLL), the most common leukemia in adults, occurs with the accumulation of mature-appearing malignant monoclonal B cells in the bone marrow, peripheral blood, or lymph node. CLL's clinical spectrum and course are very variable, with 1/3 of the cases living for more than 20 years and not requiring treatment, while 3 – 10% of them develop an aggressive 'Richter transformation'. The most common finding in physical examination is lymphadenopathy (LAP); splenomegaly and hepatomegaly can also be seen (2). CLL can involve many non-lymphoid organs. Thoracic complications are common in hospitalized patients with CLL, but data on the specific etiology and incidence are limited (3). Because of CLL's involvement, pleural, parenchymal, and airway disease may occur, as well as side effects from therapeutic agents, infections from typical or opportunistic organisms, or existing comorbidities. In early-stage asymptomatic patients, observation and 3-month follow-up are recommended instead of initiating treatment immediately. Moderate-risk (Rai Stage I and II) patients and high-risk patients (Rai Stage III and IV) or Binet Stage B and C patients benefit from treatment (4).

Pleural effusion may cause symptoms such as dyspnea, cough, and chest pain and may accompany fever and vena cava superior syndrome. Fluid may cause blunting in the costophrenic sinus on chest X-ray, which does not cause any symptoms, or it may appear as a homogeneous density covering the entire hemithorax with severe respiratory distress. In some cases, PE may be the first sign of malignancy. Thoracentesis is always necessary for the differential diagnosis of pleural effusion (PE) in patients with hematological malignancies unless the fluid is very low. Its appearance may be serous, serous, chylous, or hemorrhagic if pleural involvement is present (5).

CASE

A 58-year-old male patient with a diagnosis of chronic lymphocytic leukemia was admitted to our institution with complaints of dyspnea and hypoxia. A chest X-ray was performed in a different healthcare facility and referred to us after detecting pleural effusion in the right pulmonary lobe. At the time of admission, the patient complained of dyspnea and hypoxia, and evacuatory thoracentesis was performed in order to relieve her symptoms.

Fluid biochemistry was exudate, and pathology was benign. Tube thoracostomy was applied upon the recurrence of the fluid. The general condition of the patient was moderate. Thorax

computerized tomography (CT) revealed no pathology except minimal effusion. positron emission tomography scans (PET/CT) taken upon the recurrence of the fluid revealed a slightly increased 18 - Fludeoxyglucose (FDG – 18) uptake in the paramediastinal area of the right lung in the areas of pleural thickening compared to the surrounding tissue.

SUV max was 1.8, and surgery was considered high risk in the patient whose general condition was moderate, low effort capacity, and severe anemia. Two closed pleural biopsies were performed and the result was reported as benign. Daily drainage decreased in the patient who underwent talc pleurodesis 3 times, but it did not end. The patient was discharged with a Heimlich valve and was followed up with a drain for 45 days. Upon detection of a 5 cm solid, immobile mass on the right chest wall in control, an incisional biopsy was taken over the lesion. The oncology clinic consulted the patient, whose pathology result was malignant epithelial mesothelioma. Chemotherapy (CT) and radiotherapy (RT) was initiated.

The patient, who was followed up for 3 months for undiagnosed pleural effusion, died from a mass on the chest wall and 2 months after diagnosis of malignant mesothelioma.

DISCUSSION

Thoracic complications in CLL can be examined under 3 headings: 1) Infectious complications that are directly related to the severity of leukemia or immunodeficiency secondary to treatment, 2) Pleural pleural effusion caused by a mass or lymph node related to the localization of CLL, or due to venous or lymphatic compression. Effusions, and 3) bronchopulmonary involvement secondary to lymphocytic infiltration (6). Specific bronchopulmonary involvement due to CLL, known as bronchopulmonary pathological leukemic infiltration (BPLI), is rare; few cases have been reported in the literature. Although pneumonia is the most common thoracic complication in patients with CLL, non-infectious complications are also common. In approximately 3/4 of the cases with CLL, marked neutropenia, cellular immunity defects, and infectious complications due to immunosuppressive therapy occur during the course of the disease (7). A lung biopsy is required to reveal other forms of non-infectious parenchyma involvement in the presence of pneumonic infiltration with delayed resolution. Leukemic pleural effusion and 'Richter's syndrome' are other common thoracic involvements after pneumonia. The progression of CLL may occur as BPLI. In a series in which 2602 cases with CLL were evaluated, thoracic complications were found in 409 cases and it was reported that pneumonia was observed in 62.8%, pleural effusion with a frequency of 31.8%, and lung cancer with a frequency of 6.9%, while BPLI was observed in 5.9% of cases (8).

In another study, direct lung or pleural involvement with leukemic cells (9%) was found to be the second most common complication after pneumonia (9). Autopsy studies, on the other hand, report up to 40% lung involvement with leukemic cells in patients with CLL. However, leukemic cell infiltrates in most patients are clinically insignificant (10,11).

Multiple bilateral mediastinal LAP, mosaic perfusion, expiratory air trapping, budding tree view with centrilobular micronodules, centrilobular ground glass opacities, or homogeneous parenchymal consolidation can be observed on thorax CT. The diagnosis should be based on

bronchoalveolar lavage fluid (BAL), immunophenotype studies, and transbronchial or surgical lung biopsy accompanied by imaging (12).

Pulmonary involvement in CLL can occur in various ways, primarily in patients with advanced disease who have a previous treatment history for CLL. Infectious causes should be excluded in cases. It has been reported that there is no correlation between pulmonary leukemic infiltrates and peripheral blood absolute lymphocyte counts (13). In the series of Carmier et al., progressive lymphocytosis (median 27.2x10 9 cells), bilateral axillary, inguinal LAP, mediastinal LAP, and lymphocytic pulmonary infiltrate have been observed in all cases (14). High lymphocyte counts have been reported in cases with high rations. In general, an intense B-CLL infiltration with peribronchial and perivascular distribution is detected in pulmonary biopsies. Specific leukemic infiltration with CLL actually indicates true extranodal tissue involvement, not a non-specific "temporary effect" secondary to increased permeability due to continued inflammation and host response (13). Combined chemotherapy is recommended for CLL according to the severity of pleural effusion. In the presence of respiratory symptoms, specific therapy should be administered regardless of the extent of the peripheral blood lymphocyte count. Antineoplastic therapy is an appropriate treatment approach when BPLI is diagnosed, especially when infection is excluded (15).

Thoracentesis is the first interventional approach in a patient with an unspecified effusion. Despite the improvements in the diagnostic accuracy of imaging methods, cytology or tissue sample examination is required to confirm the diagnosis of MPE. Initial thoracentesis is diagnostic as well as therapeutic, as most MPE patients are dyspneic. Pleural fluid should be sent for cell count, total protein, lactate dehydrogenase (LDH), glucose, amylase, pH, and cytology. At least 50 mL of fluid sample should be obtained for cytological evaluations (15).

The efficiency of cytological examination in the diagnosis of MPE is variable. Although it reaches 60%, especially in the diagnosis of metastatic adenocarcinoma, it is unfortunately at a low rate of approximately 20% in the diagnosis of mesothelioma. This is because it is difficult to distinguish between normal, reactive, and malignant mesothelial cells. However, this rate may increase to 70% in advanced mesotheliomas with visceral pleural involvement (15).

Although it has been reported that the diagnostic value increases with repeated thoracentesis, the next diagnostic procedure after the first or second negative cytology should be thoracoscopic, which has a sensitivity of 90%. Positive standard pleural cytology may not differentiate between pleural adenocarcinoma, mesothelioma, lymphoma, or reactive lymphocytosis (15).

The treatment of malignant pleural effusion depends on the etiology of the effusion, lung reexpansion, general condition of the patient, symptoms, and life expectancy. With systemic therapy, MPE can be controlled in lymphoma, breast, prostate, ovarian, thyroid cancer, small cell lung cancer, and germ cell tumors. Radiotherapy may be beneficial in mediastinal lymph node involvement. The main goal in the treatment of patients with malignant pleural effusion should be to improve the patient's symptoms with minimal hospitalization and complications. Unfortunately, many patients do not respond to systemic therapy, so other treatment

modalities must be considered. Today, thoracentesis, pleural catheter/pigtail catheter insertion, chest tube, and pleurodesis are used to treat symptomatic MPE (15).

CONCLUSION

In this case, we wanted to emphasize the importance of performing a large-scale open pleural biopsy with absolute vision in recurrent pleural effusions, where fluid cytology, biochemistry, and imaging methods can be misleading and increase the awareness of clinicians.

Abbreviations

BAL : Bronchoalveolar lavage
BPLI : Bronchopulmonary pathological leukemic infiltration
CLL : Chronic lymphocytic leukemia
CT : Chemotherapy
CT : Computerized tomography
FDG – 18 :18 - Fludeoxyglucose
LAP : Lymphadenopathy
LDH : Lactate dehydrogenase
MPE : Malignant pleural effusion
PE : Pleural effusion
PET/CT : Positron emission tomography
RT : Radiotherapy
SUV max : Standardized uptake value

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Competing interests: The authors declare that they have no competing interests.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution.

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Posterior Reversible Encephalopathy Syndrome: Case Report

Posterior Reversibl Ensefalopati Sendromu: Vaka Raporu

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a neurological disease characterized by a range of neurological signs, symptoms and different neuroimaging findings reflecting vasogenic edema. Etiology of PRES may include hypertension, eclampsia/preeclampsia, sepsis, immunosuppressive agents, chemotherapy, collagen-vascular diseases and renal failure. Although SLE is a rare cause of PRES, endothelial damage and increased blood pressure due to vasculitic involvement are thought to play a role in the etiology. In this case report, a 38-year-old patient with a diagnosis of SLE who has a hypertensive attack and visual loss was presented.

Keywords: Posterior Reversible Encephalopathy Syndrome, Systemic Lupus Erythematosus, Hypertension.

Özet

Posterior geri dönüşümlü ensefalopati sendromu (PRES), bir dizi nörolojik belirti, semptom ve vazojenik ödemi yansıtan farklı nörogörüntüleme bulguları ile karakterize nörolojik bir hastalıktır. PRES etiyolojisinde hipertansiyon, eklampsi/preeklampsi, sepsis, immünosüpresif ajanlar, kemoterapi, kollajen- vasküler hastalıklar ve böbrek yetmezliği yer alabilir. SLE, PRES'in nadir bir nedeni olmasına rağmen, vaskülitik tutuluma bağlı endotel hasarı ve artmış kan basıncının etiyolojide rol aldığı düşünülmektedir. Bu olgu sunumunda 38 yaşında SLE tanısı olan, hipertansif atak ve görme kaybı ile başvuran bir hasta sunuldu.

Anahtar Kelimeler: Posterior Geri Dönüşümlü Ensefalopati Sendromu, Sistemik Lupus Eritamatozus, Hipertansiyon.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a neurological disease characterized by a range of neurological signs, symptoms and different neuroimaging findings reflecting vasogenic edema. The reason why it is called reversible is that clinical neurological findings and imaging findings improve hours or days after treatment is started (1).

Clinical conditions that cause changes in blood pressure, drugs, dysautonomia, chemotherapy, and discontinuation of antihertensive treatment can be considered as risk factors for the development of PRES syndrome (2). The clinical symptoms of toxicity are extensive, but most commonly headache, mental status changes, seizures, nausea/vomiting, and focal

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neurological disorders are observed (3). Visual findings such as hemianopia, cortical blindness, visual hallucinations, and visual acuity deterioration may occur in approximately two-thirds of PRES patients due to occipital lobe involvement (4).

This case report aims to, present a patient with a diagnosis of Systemic Lupus Erythematosus (SLE) who presented to the emergency with sudden vision loss, nausea, vomiting and confusion.

CASE

A 38-year-old patient, who had been diagnosed with SLE for 7 years, presented to the emergency department with sudden vision loss, nausea, vomiting and confusion. It was learned that the patient had applied to the emergency department with 2 hypertensive attacks before, used ramipril 5 mg irregularly, and did not have regular follow-up and treatment. In the neurological examination of the patient, her consciousness was latergic and her orientation-cooperation was limited. In the pupillary midline, the light reflex was taken directly or indirectly. She could not cooperate with her eye movements, could not count fingers in one meter, and did not have facial asymmetry. All four extremities were spontaneously mobile, plantar reflex bilateral flexor and there was no nuchal rigidity.

The patient's blood pressure was 210/110 mmHg and fever: 36.9°C. Electrocardiogram was normal. In laboratory tests, white blood cell: 8.6 K/uL (4-10), hemoglobin: 13.1 g/dL (11-17), platelet: 310 K/uL (100-380), C-reactive protein: 6.2 mg/L (0-5), urea: 41.2 mg/dL (8-20), creatinine:1.47 mg/dL (0.51-0.95). Liver function tests, electrolytes, and thyroid function tests were normal. Complete urinalysis was normal. In brain magnetic resonance imaging (MRI), fluid-attenuated inversion application recovery (FLAIR) sections, symmetrical hyperintense vasogenic edema findings in bilateral occipitotemporal regions were observed (A). Apparent diffusion coefficient (ADC) map showed high signal (B). MRI angiography and venography were normal. (Figure 1)

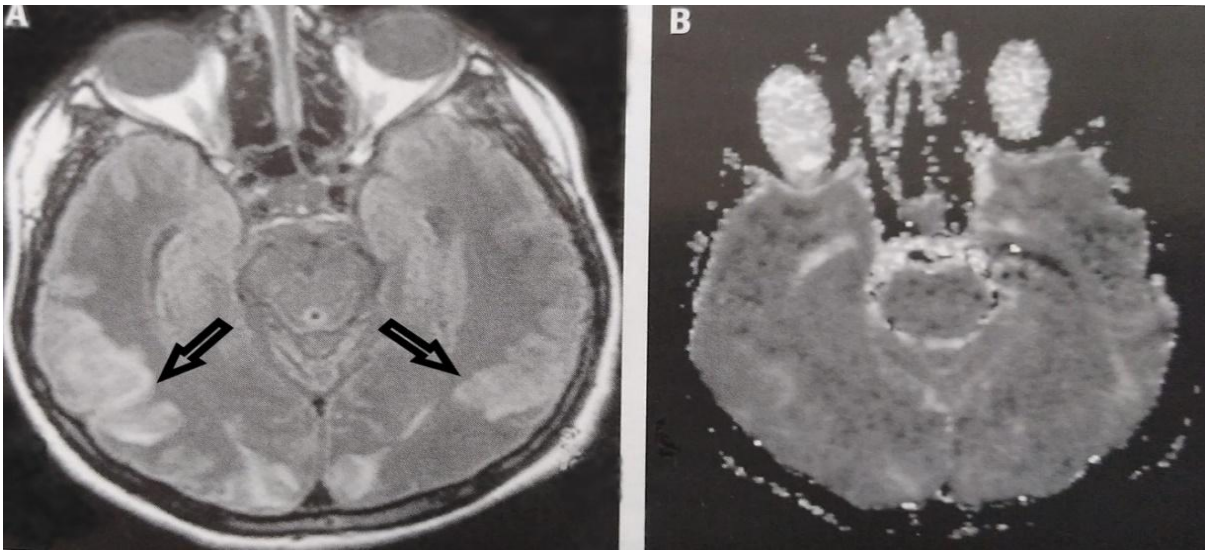

Figure 1. A. Fluid-attenuated inversion application recovery (FLAIR) sections. Symmetrical hyperintense vasogenic edema findings in bilateral occipitotemporal regions. B. Apparent diffusion coefficient (ADC) map showed high signal

The diagnosis of PRES was made by evaluating the patient's anamnesis, clinical findings and imaging. The patient was admitted to the neurology service and intravenous nitroglycerin

treatment was started to control blood pressure. Blood pressure values were gradually reduced and blood pressure regulation was achieved at the end of 12 hours. The patient was given 10 mg of mannitol 3 times on the first day as antiedema treatment, then the daily dose was tapered and discontinued. Since the patient could take it orally, 150 mg acetylsalicylic acid treatment was added. The patient's confusion resolved within 12 hours, and visual impairment almost completely resolved within 6 days. Cranial MR findings obtained at the end of a week showed almost complete improvement.

DISCUSSION

In this case report, we aimed to present a patient with a diagnosis of SLE who presented with a hypertensive episode with vision lossand confusion in the clinic and diagnosed with PRES.Although the pathophysiology of PRES is not known exactly, its etiology includes hypertension, eclampsia/preeclampsia, sepsis, immunosuppressive agents, chemotherapy, collagen-vascular diseases, and kidney failure (5). Our patient had a diagnosis of SLE and her blood pressure values were very high. Similarly, Sudan et al. reported a 32-year-old patient with a diagnosis of PRES who presented with a hypertensive episode and acute vision loss in both eyes (6).

PRES is a reversible picture characterized by segmental vasoconstriction and vasodilation in small cerebral vessels, often resulting from cerebral vascular tone irregularity (1). In its pathophysiology, disruption in cerebrovascular autoregulation and the resulting vasogenic edema are the main causes (7). Another reason is endothelial dysfunction caused by circulating endogenous or exogenous toxins (8). Although SLE is a rare cause of PRES, endothelial damage and increased blood pressure due to vasculitic involvement are thought to play a role in the etiology (9).

Brain MRI findings in patients with PRES characteristically show vasogenic edema. The most common neuroimaging finding is bilateral focal edematous areas in the frontal and inferior temporal-occipital junctions, especially in the parietal and occipital lobes (1). In our case, we observed hyperintense areas showing vasogenic edema in bilateral occipitotemporal regions in FLAIR sequences, consistent with the literature.

The primary goal in PRES treatment is to address the underlying cause, such as lowering blood pressure, taking antiepileptics or correcting electrolyte disturbances with sedation, hydration. In cases with acute hypertension, blood pressure should be reduced gradually, since rapid correction of blood pressure may lead to coronary, renal and cerebral ischemia (3).

In conclusion, late diagnosis or inadequate treatment in PRES may contribute to long-term sequelae such as permanent neurological disability, progressive brain edema, intracranial hemorrhage, and death. PRES should be considered in the differential diagnosis of patients presenting with hypertensive episodes and atypical clinical findings in SLE.Early diagnosis and correct interventions are crucial to achieve a favorable clinical outcome, as they can rapidly improve clinical symptoms and radiological findings.

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Conflict of interest: None declared.

Informed consent: The patient was informed for publication of the case report andaccompanying imagesconsent was obtained.

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Ascending Aorta Saccular Aneurysm: An Unexpected Reason For Acute RCA Occlusion

Asendan Aort Sakküler Anevrizması: Akut RCA Oklüzyonu İçin Beklenmedik Bir Neden

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Abstract

Saccular aortic aneurysms are rare pathologies which are true aneurysms that contain all histological layers of the aorta. Although an aortic diameter of 3 cm or more is generally accepted as an aneurysm, the surgical indication age is usually above 5 cm. SAA, on the other hand, can be operated by its diagnosis, since they are dysmorphic aneurysms and more prone to rupture regardless of their diameters. As in our case, a SAA may cause acute coronary syndromes, patients may apply with acute myocardial infarction. Although a SAA involving a coronary ostia is a very rare cause of acute coronary syndrome, it still should be kept in mind. In November 2022, A 57 year old male patient with inferior AMI due to an occlusive complication of a sacculary aneurysm involving the right coronary artery (RCA). Consequently, the patient was operated urgently. Aneurysm was excised and a graft coronary artery bypass was performed to RCA. Postoperative follow-up and treatment were uneventful and the patient was discharged on the 11th postoperative day.

Keywords: Acute Miocard Infarction, RCA Occlusion, Aortic Saccular Aneurysm.

Özet

Asendan aorta sakküler anevrizmaları nadir görülen patolojilerdir. Aortanın tüm histolojik katmanlarını içerir. Genellikle aorta çapı 3 cm ve üzerinde olması anevrizma olarak kabul edilse de cerrahi endikasyonu genellikle 5 cm ve üzeri olarak değerlendirilir. Sakküler anevrizmalar ise dismorfik anevrizmalar olmaları nedeniyle çaptan bağımsız olarak opere edilebilirler. Zira, spontan rüptür ve komplikasyon riski fuziform anevrizmalara göre daha yüksektir. Bizim vakamızda olduğu şekliyle akut koroner sendroma neden olabilirler. Koroner ostiumları içine alan bir sakküler anevrizma akut koroner sendromlar için nadir bir neden olsa da akılda bulundurulmalıdır. Kasım 2022'de, 57 yaşında erkek hasta acilde akut inferiyor miyokard infarktüsü olarak tanı aldı ve yapılan tetkiklerinde sağ koroner arteri de içine alan sakküler aortik anevrizmaya bağlı oklüzif komplikasyon olduğu görüldü ve acil şartlarda operasyona alındı. Postoperatif takip ve tedavisi sorunsuz seyreden hasta 11. gün taburcu edildi.

Anahtar Kelimeler: Akut Miyokardiyal İnfarkt, RCA Oklüzyonu, Aortik Sakküler Anevrizma.

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INTRODUCTION

Thoracic aortic aneurysms is reported as 3-4% (1) among reported deaths. The cause changes depending on patient age, connective tissue diseases, congenital causes such as bicuspid aortic valve, inflammatory diseases, high blood pressure and various syndromes are common. Generally, it occurs due to a medial degeneration of the elastic wall of the aorta for a non-inflammatory reason. SAA constitutes a less common sub-group. Etiology is often secondary to infectious pathologies where the risk of rupture and complications is higher. Infective endocarditis, syphilis, fungal infections, AIDS and iatrogenic causes are the most frequent reasons.

In cases of SAA located in the ascending aorta, the surgery to be performed varies due to the presence of annuloaortic ectasia, involvement of Valsalva sinuses and aortic valve insufficiency. Generally, the Bentall Procedure is preferred. As in our case, focal excision of the SAA is rarely sufficient. We performed aneurysmectomy and RCA saphenous graft coronary bypass.

CASE REPORT

A 57 year old female patient was admitted to the emergency department with increasing severity of chest pain, palpitation and discomfort. Coronary angiography (CAG) performed rapidly due to inferior AMI findings on ECG and Troponin I value being too high to be measured above 50,000 ng/L.

In CAG (Figure 1) left system was intact. The right RCA ostium could not be seated. Therefore, nonselective aortic root angiography for aortic root and RCA were visualized. A saccular aneurysm observed in the aortic root on the right side. RCA originated from this aneurysm. RCA antegrade filling was extremely weak. Perfusion was from the left, retrogradely.

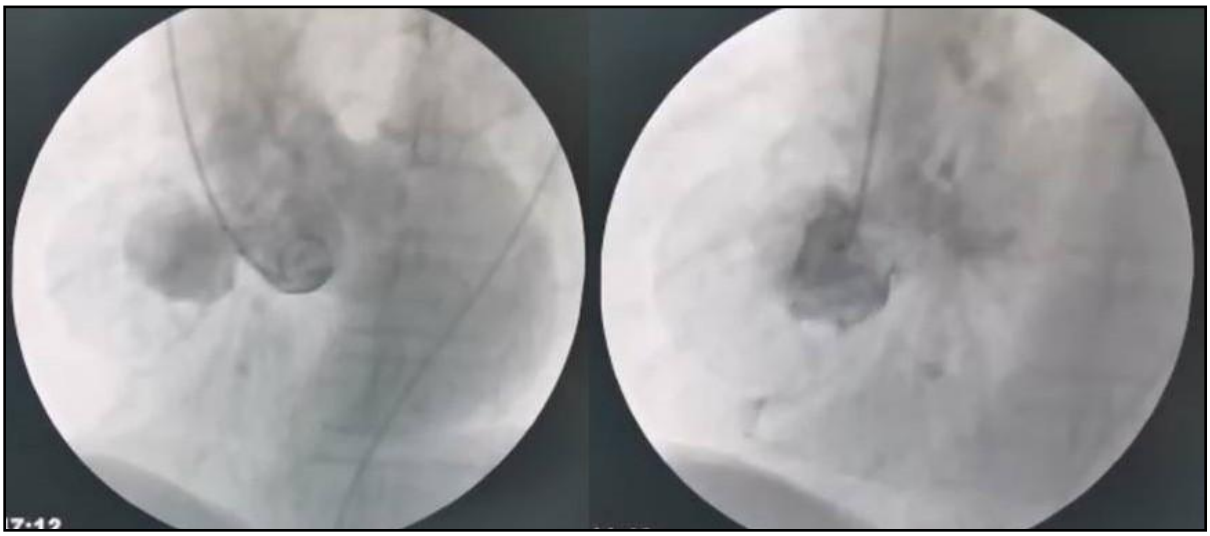

Figure 1. In CAG Left System

In preoperative transthoracic echocardiography (Figure 2); there was no aortic valve pathology and aortic valve insufficiency. Thus, we decided a valve-sparing surgery rather than the Bentall procedure.

In IV contrast thorax computerized tomography (CT) (Figure 3 a). SAA was observed in 4x5x4 cm diameters on the right sinotubular junction. No other vessel pathology was observed.

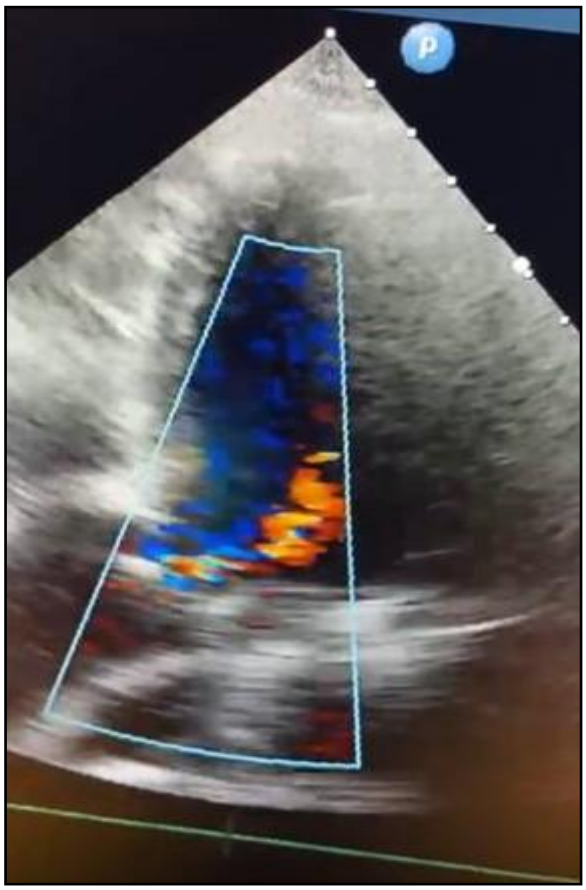

Figure 2. Preoperative Transthoracic Echocardiography

In figure 3 (b), postoperative excised aneurysm with normal aortic lumen.

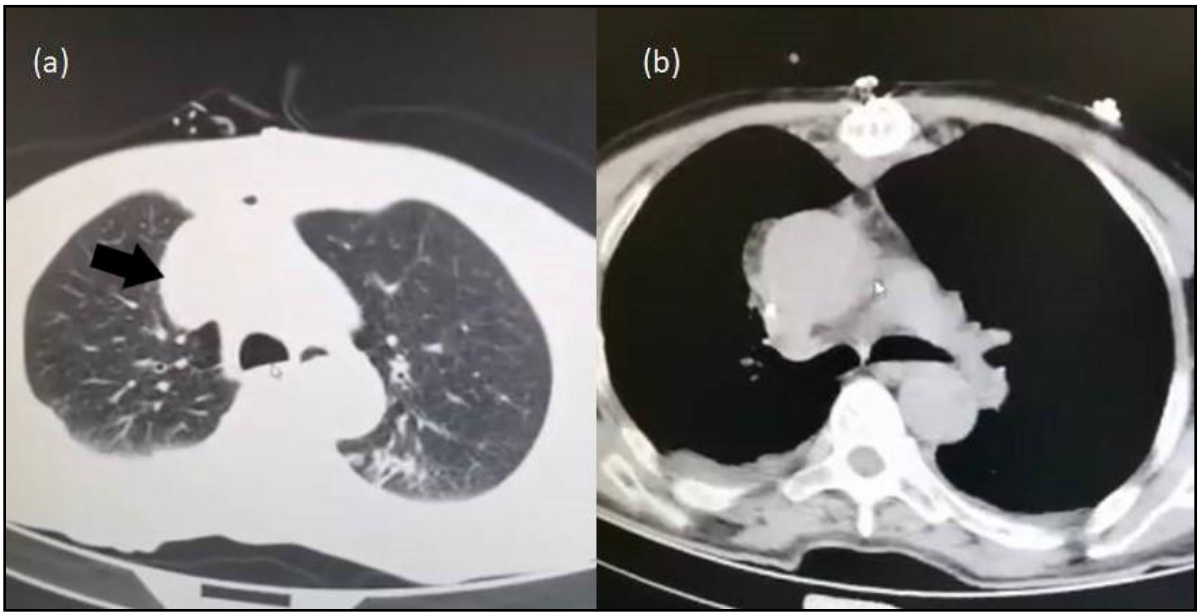

Figure 3. IV Contrast Thorax Computerized Tomography (CT) (Figure 3 A), Postoperative Excised Aneurysm With Normal Aortic Lumen (Figure 3 B)

Selective RCA saphenous graft bypass with aneurysmectomy and patchplasty was decided for the patient, via CPB.

After sternotomy, the pericardium was opened and SAA was revealed (Figure 4).

Figure 4. After Sternotomy, the Pericardium was Opened and SAA was Revealed

After aortic cross-clamping and cardioplegic arrest, the SAA was totally excised. We observed that the aortic valve and sinotubular junction were intact (Figure 5).

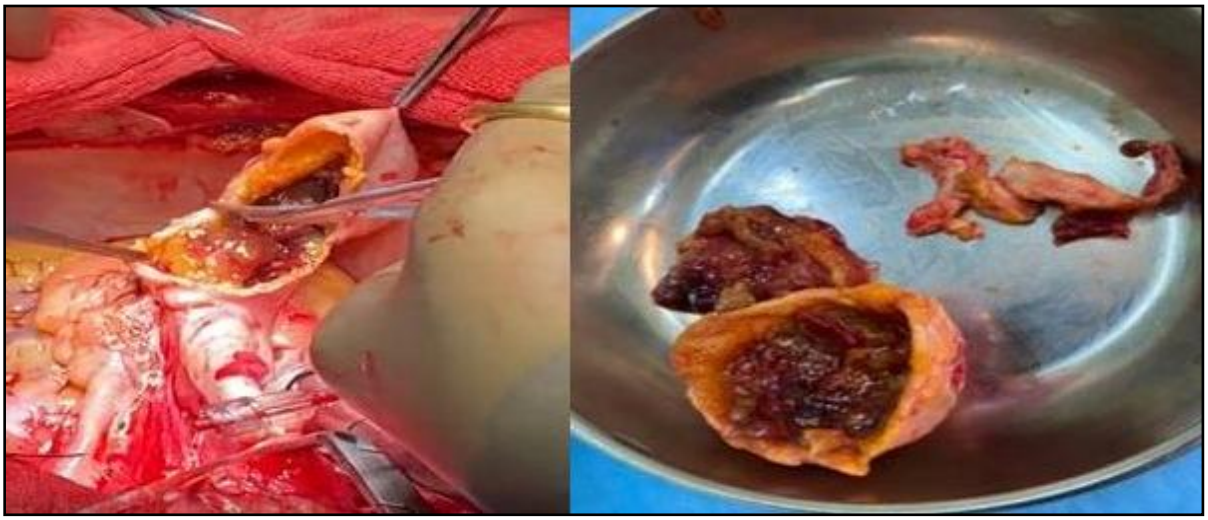

Figure 5. Observed that the Aortic Valve and Sinotubular Junction were Intact

SAA area was primarily repaired with pledged sutures with a PTFE graft and patchplasty was performed (Figure 6).

Sequentially, a saphenous graft RCA was anastomosed end-to-side to RCA trunk.

Proximal anastomosis was placed in the intact part of the ascending aorta.

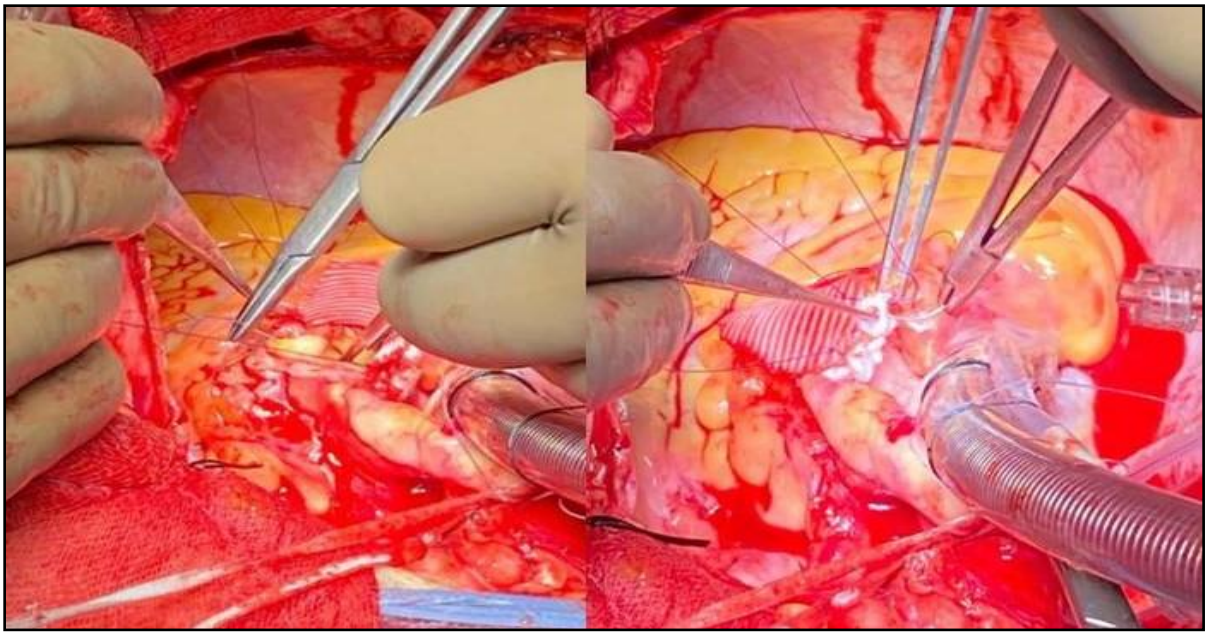

Figure 6. SAA area was Primarily Repaired with Pledged Sutures with a PTFE Graft and Patchplasty was Performed

The operation was terminated conventionally. It was confirmed that there was no bleeding from the patchplasty. The operation was completed complication free. Following 3 days of ICU, he was discharged on the 11th postoperative day.

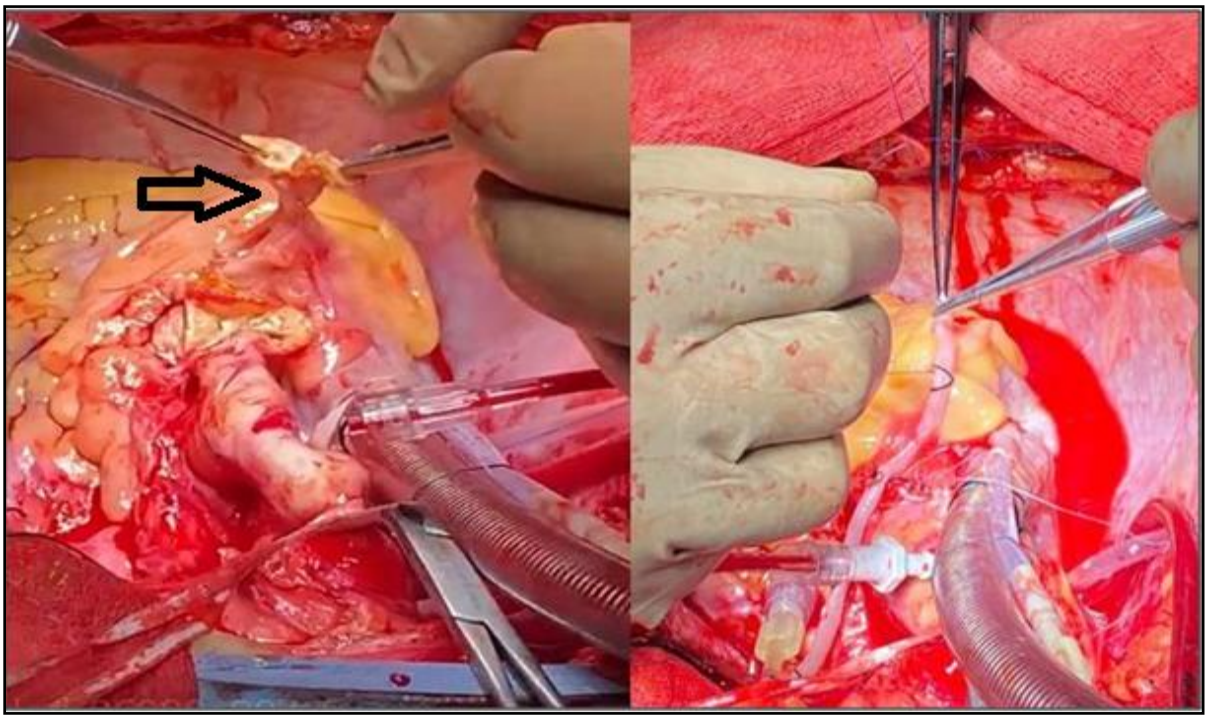

Figure 7. The Operation Was Terminated Conventionally

Histopathological samples were studied with a calsified soft tissue free of any malignant feature by 4x1.5x2 cms in diameter. Furthermore, characteristic histopathological findings of a hereditary connective tissue disease were not detected. This histological evaluation was obtained by Hematoxylin and Eosin (H&E) X10 staining of tissue and cell sections (Figure 8).

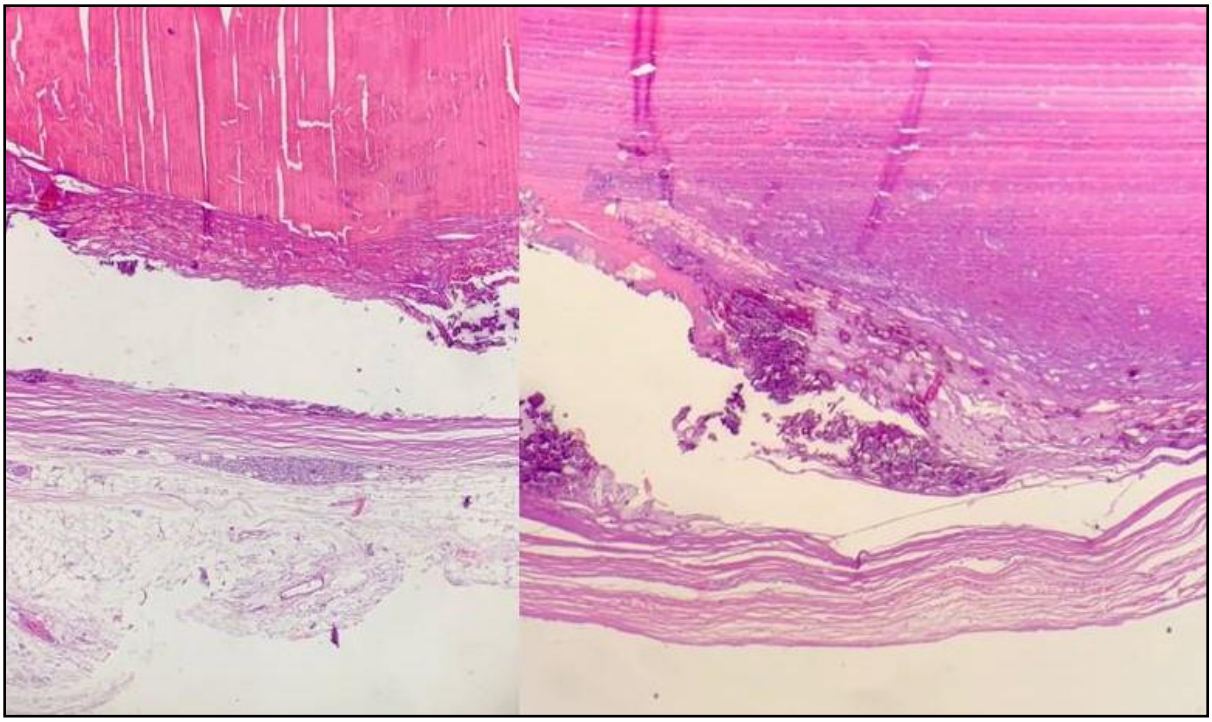

Figure 8. Histological Evaluation

DISCUSSION

Within the classification, aneurysm may include aortic root, ascending aorta, aortic arch, descending aorta and different associations. The co-existence of aortic root dilatation is called 'annuloaortic ectasia'. In different scientific publications, it has been reported that the incidence of thoracic aneurysm is between 3-5% with increasing imaging examination method efficiency. Idiopathic and non-inflammatory aneurysms are usually defined in adults and with connective tissue diseases. Bicuspid aorta, aortic dissections, hypertension and several syndromes such as Ehlers-Danlos, Marfan and Loeys-Dietz can be counted in etiology. Aneurysms formed after inlammatory processes occur at a later age with aortitis. Causes such as giant cell arteritis syndromes and Takaysu arteritis are common. The female to male ratio does not show significant differences (1).

Aortic aneurysms can be divided into two main groups morphologically; fusiform and saccular. Our patient had a saccular aneurysm in ascending aorta. Among the aetiological factors of SAA, vasculitides with a high inflammatory component, bacterial infections, fungal infections, iatrogenic trauma and to a lesser extent, syphilitic aortitis can be listed. Our case did not have a recent infectious status. He also did not describe a chronic connective tissue disease. There was no intraluminal intervention except for a coronary angiography history about a year ago.

Absence of annular and/or sinotubular dilatation and intact aortic valves positively affected our surgical risk.

The presence of acute or chronic severe inflammatory diseases were also stated as among the causes of increased mortality. Bicuspic aorta is one of the most common congenital cardiac defects in 1% of the population. There is a high familial tendency when present with aortic aneurysms. In this condition, it reveals an autosomal dominant character (2). Replacement of the aortic root and/or aortic valve complicates the surgical management. We were able to perform a direct aneurymectomy with CPB. Subsequently, the SAA area was primarily

repaired with a vascular patch. The RCA orifice was totally occluded because it was in the aneurysmal sac. Therefore, in the last stage of our surgery, native RCA was ligated proximally and occluded. Then, CABG was performed with a saphenous vein graft via aorto-coronary end-to-side anastomosis. The saphenous graft was observed as working efficiently after CPB was terminated.

Since our patient did not have a mycotic infection, connective tissue disease or a syphilitic status, the thought that it was an aneurysm that developed directly after an aortic trauma during a previous coronary angiography attempt was dominant, but naturally, it was not possible to present any definitive evidence on this subject. Although aneurysms that are presented due to catheter trauma are mostly reported as pseudoaneurysms. But a true aneurysms involving all layers of the aortic wall may also occur, as in our case (3).

In the histopathological examination, chronic connective tissue disease, acute or chronic inflammatory processes were ruled out in tissue samples stained with H&E. Therefore, the aneurysm that we excised was classified as a noninflammatory true aneurysm.

In non-inflammatory etiologies, medial degeneration, which is the basic physiopathological picture, can be found in the wall of the aorta (4). Medial degeneration is classified as mild, moderate and severe. It is directly related to the risk of rupture. In severe cases, extracellular matrix changes are also added to the picture and the resistance of the aortic vessel wall to pressure decreases. Elastic fiber loss and/or fragmentation in the media layer is also added to the condition histopathologically. The aortic wall erodes and the risk of spontaneous rupture increases.

Since the intraluminal pressure distribution is scattered in an aneurysm with saccular morphology, as in ours, luminal wall resistance due to histopathological disorders progresses much more rapidly towards dissection. In particular, arterial hypertension is the most important triggering mechanism. Moreover, the highest peri-operative mortality rates occur in aneurysms due to mycotic infections. Almost all of these patients have sepsis and related syndromes (5).

In conclusion, the prognosis of aneurysm depends on its size, localization, accompanying pathologies, and the presence of arterial hypertension. When dissection and rupture occur, the situation is usually incompatible with life. In fusiform aneurysms, 55 mm is generally accepted as the surgical indication margin. However, as in our case with saccular aneurysms with a higher risk of rupture, there is no surgical criterion to be determined by a precise aneurysm diameter. We believe that surgery should be planned with the detection of SAA.

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Informed Consent: The patient was informed for publication of the case report andaccompanying imagesconsent was obtained.

Ethical Declaration: The study was conducted in accordance with the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”. Ethics committee approval has been granted from our institution.

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