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BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

CONTENTS / İÇİNDEKİLER

ORIGINAL RESEARCHES / ARAŞTIRMALAR

REVIEWS / DERLEMELER

CASE REPORTS / OLGU SUNUMLARI

CONTENTS / İÇİNDEKİLER

LETTER TO THE EDITOR / EDİTÖRE MEKTUP

INDEX / İNDEKS

ORIGINAL RESEARCH

Bagcilar Med Bull 2024;9(4):225-231
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Impact of the COVID-19 Pandemic on Childhood Obesity Prevalence

COVID-19 Pandemi Sürecinde Çocukluk Çağı Obezite Prevalansının Etkisi

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Abstract

Objective: The global obesity pandemic among children was defined at the beginning of the millennium. It has been shown that childhood obesity has increased with the deterioration of behavioral and environmental factors during the Coronavirus disease-2019 pandemic in various studies. This study aimed to evaluate childhood obesity rates and their underlying causes in İstanbul.

Method: Children born in İstanbul in 2015 and who continue to reside in İstanbul with Turkish Nationality were our target population. The study population comprised 241,121 children, and the sample was calculated as 196 children by using World Health Organization online calculator, assuming a prevalence of 15% with 95% confidence interval and 5% margin of error. A stratified cluster sampling approach was used to select participants from every district in İstanbul. Parents were contacted by telephone, and those who agreed to participate in the study were invited to the family health centers where they were registered. The frequency analysis, chi-square test, t-test, and correlation analysis were conducted. The statistical significance level was set as p<0.05.

Results: Of the children, 36.6% (n=70) were obese and overweight (obesity prevalence was 23.3%); and among those 60% (n=42) were female. Father's low educational level (p=0.016), eating 3 main meals more often (p=0.004), and regular consumption of packaged food regularly (p=0.034) were significantly associated with being overweight or obese. There was a significant increase in the body mass index of children in 2021 compared with 2019 (t=47,24; p<0.001).

Conclusion: During the pandemic, childhood obesity was increased among six-year-old children in İstanbul. Considering that the probability of the occurrence of pandemics and disasters will increase in the coming years, public health interventions such as applications to increase children's physical activity should be planned and prepared.

Keywords: Childhood obesity, COVID-19, overweight

Öz

Amaç: Bu milenyumun başında çocuklar arasında obezite salgını küresel bir boyut aldı. Koronavirüs hastalığı-2019 pandemi sürecinde yapılan çalışmalarda, davranışsal ve çevresel faktörlerin bozulmasıyla birlikte çocukluk çağı obezitesinin arttığı gösterilmiştir. Bu çalışmada amacımız, İstanbul'da çocukluk çağı obezite oranlarını ve altında yatan nedenleri değerlendirmektir.

Yöntem: 2015 yılında İstanbul'da doğan ve İstanbul'da ikamet etmeye devam eden Türkiye Cumhuriyeti vatandaşı çocuklar hedef kitlemizdi. Çalışma evreni 241.121 çocuktan oluşmakta olup, örneklem Dünya Sağlık Örgütü çevrimiçi hesaplayıcısı kullanılarak %95 güven aralığı ve %5 hata payı ile %15 prevalans varsayılarak 196 çocuk olarak hesaplanmıştır. Katılımcıların seçiminde İstanbul'un her ilçesinden tabakalı küme örnekleme yaklaşımı kullanılmıştır. Ebeveynlere telefonla ulaşılmış ve çalışmaya katılmayı kabul edenler kayıtlı oldukları aile sağlığı merkezlerine davet edilmiştir. Frekans analizi, ki-kare, t-testi ve korelasyon analizi yapıldı. İstatistiksel anlamlılık düzeyi p<0,05 olarak kabul edildi.

Bulgular: Çocukların %36,6'sı (n=70) obez ve fazla kiloluydu (obezite prevelansı %23,3); ve bunların %60'ı (n=42) kızdı. Babanın eğitim düzeyinin düşük olması (p=0,016), 3 ana öğünü beslenmesi (p=0,004) ve düzenli olarak paketli gıda tüketmesi (p=0,034) fazla kilolu veya obez çocuk olma ile anlamlı düzeyde ilişkiliydi. 2021 yılında çocukların vücut kitle indeksinde 2019 yılına göre anlamlı bir artış oldu (t=47,24; p<0,001).

Sonuç: Pandemi döneminde İstanbul'da 6 yaşındaki çocuklarda çocukluk çağı obezitesinde artış gözlendi. Önümüzdeki yıllarda pandemi ve afetlerin ortaya çıkma ihtimalinin yüksek olduğu göz önünde bulundurularak çocukların fiziksel aktivitelerini artırmaya yönelik uygulamalar gibi halk sağlığı müdahaleleri planlanmalı ve hazırlanmalıdır.

Anahtar kelimeler: COVID-19, çocukluk çağı obezitesi, fazla kiloluluk

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Introduction

A global pandemic of obesity among children was defined, with a significant increase in obesity prevalence at the beginning of the millennium. In parallel, an increase in obesity-associated early clinical onset-chronic diseases was determined (1). Childhood obesity, which was initially described as a problem in high-income countries, has now become a global public health problem that affects the whole world. In 2016, 124 million children and adolescents were classified as obese, representing a 10-fold increase compared with the 1970s (2,3). In the Turkey Nutrition and Health Survey, which was conducted in 2010, obesity and overweight rates were 26.4% in the 0-5 age group and 22.5% in the 6-18 age group (4).

Childhood obesity can have major effects on physical health, social and emotional well-being, and self-esteem in children. Previous studies have shown that obese children have a higher possibility of developing fatty liver disease, sleep apnea, type 2 diabetes, asthma, cardiovascular disease, hypercholesterolemia, cholelithiasis, glucose intolerance and insulin resistance, skin conditions, menstrual abnormalities, impaired balance, and orthopedic problems. Overweight and obese children can be bullied, discriminated against, or socially marginalized. These negative social interactions may result in low self-esteem and self-confidence. Poor academic performance and poor quality of life are the other consequences of childhood obesity (5). Furthermore, obese children are more likely to work in lower-paid and poorly-employed jobs in adulthood (3).

Obesity develops in combination with one or more genetic, behavioral (emotional state), and environmental factors. It has been observed that childhood obesity has increased with the deterioration of behavioral and environmental factors during the Coronavirus disease-2019 (COVID-19) pandemic (6,7). During the COVID-19 pandemic, lockdowns and movement restrictions increased the consumption of non-perishable and processed foods, decreased physical activity, and difficulties in accessing fresh foods and health care services were some of those factors. Quarantine, home confinement, and social distancing caused an increase in psychological stress and stress-related eating. In-person contact with classmates/teachers and access to physical activity decreased due to school closures. Increasing screen time and disrupted sleep patterns also negatively affected eating habits (8). In this population-based study, we aimed to evaluate childhood obesity rates and their underlying causes; also reveal the change in the obesity prevalence during the COVID-19 outbreak in İstanbul.

Materials and Methods

The study was planned in two stages, retrospectively and prospectively, to include children who were born and still residing in İstanbul with Turkish nationality. Although there are many studies on school-age childhood and adolescence in the literature, obesity studies on play-age children are less common. In our study, measurements at the ages of 4, 5, and 6 years, including during childhood, were used.

Study Population

According to Turkish Institute of Statistics data, 241,121 children were born in İstanbul born in 2015 with Turkish nationality is 241,121. The target population of this study is composed of children who were born in İstanbul in 2015 and who continue to reside in İstanbul. The sample was formed by weighting the data according to district populations to create the target population representation. The sample size was calculated as 196, by using World Health Organization online calculator, assuming a prevalence of 15% with 95% CI and 5% margin of error. A stratified cluster sampling approach was used in the selection of participants from every district of İstanbul (a total of 39 districts in İstanbul, the district of Adalar was not included in the study due to its low population). All children whose parents provided written permission to participate in the study were included. Instead of the people who did not consent participating in the study, the previous respondents on the list were called.

Data Gathering Tool and Process

Routine well-child examinationsare performed by family physicians nine times from the age of 0 to 1 year old starting at birth, twice a year at age 1-3, and once a year at age 3-5 in Turkey, and this information is recorded on a national health system (NHS) database. Birth information and the four- and five-year health data of the children were obtained from the NHS. Six-year-old readings were performed by the researchers of this study prospectively.

Parents were contacted by telephone, and those who agreed to participate in the study were invited to the family health centers where they were registered. Through a questionnaire, the socio-demographic information of the participants, such as birth information, nutrition, daily eating habits, periods of screen exposure, and the mother and father's height and weight, were recorded. Children's weight measurements were performed by researchers using the Tanita SC 240 model, and their heights were measured using measuring plates affixed to the wall.

Obesity was determined by calculating the body mass index (BMI). BMI indicates whether a child's weight is right for their height, and the result is given as a percentile. The BMI calculation takes into account age, sex, height, and weight. Children with 95th percentile or higher are considered obese, and 85th to 95th percentile are considered overweight.

Statistical Analysis

The data were analyzed using SPSS Version 22.0. Frequency analysis was conducted; also, the relations between variables were evaluated using chi-square, t-test, and correlation analysis. The statistical significance level was set as $p<0.05$.

Ethics

This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2000) and was approved by the Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey (2021.04.131).

Results

The study included 191 children. The characteristics of the children and their families are presented in Table 1.

Of the children who participated in the study, 8.9% (n=17) reported having chronic diseases, such as thalassemia, allergic asthma, vesicoureteral reflux, glucose-6-phosphate dehydrogenase deficiency, hearing loss, congenital adrenal hyperplasia, and congenital heart disease. Among the children, 56.5% (n=108) were born by cesarean section, and 43.5% were born naturally. Nutritional information at birth and after birth of the children included in the study are presented in Table 2.

It has been stated that 46.3% of children started consuming packaged foods after age 2, and 39.2% started after age 1. The average time children spend per day in front of the television is 1.83±1.45 hours and on tablets is 2.59±2.05 hours. The daily diet and activity habits of the children included in the study are presented in Table 3.

The average age of the mothers of the children who were participating in the study was 35.1±5.8 years and their average BMI was 27.55±4.8, while these were 38.41±5.7 and 27.26±3.6 for the fathers, respectively. There were no significant relationships between maternal and paternal BMI and children's BMI.

Of the children, 36.6% (n=70) were obese and overweight (obesity prevelance was 23.3%); and among those 60% (n=42) were female. There is no significant differences in BMI measurements between girls and boys. Some of the participants' BMI measurements are presented in Table 4.

The children's BMI mean was 15.74±1.81 (10.85-23.27) in 2019, 15.81±2.2 (9.26-27.21) in 2020, and 16.70±3.2 in 2021 (11.75-29.17). Evaluation of children's growth measurements in 2021 is presented in Graphic 1.

Table 1. The demographic of the children and their families

Variables		n	%
Gender	Female	106	55.5
	Male	85	44.5
Family income status	Income less than expense	115	60.2
	Income to expensein balance	76	39.8
Health insurance	Yes	182	95.3
	No	9	4.7
Maternal education level	Primary education	130	68.1
	High school	39	20.4
	University and above	22	11.5
Paternal education level	Primary education	109	57.1
	High school	46	24.1
	University and above	36	18.8
Maternal work status	Working	25	13.1
	Not working	161	86.9
Paternal work status	Working	184	96.3
	Not working	7	3.7
Total number of children in the family	One child	15	7.9
	2 children	88	46.1
	3 children	61	31.9
	4 and more	27	14.1
Long-term disease in the child	Yes	18	9.4
	No	173	90.6
COVID-19 infection status	Yes	1	0.5
	No	190	99.5

COVID-19: Coronavirus disease-2019

Table 2. Nutritional information at birth and after birth

	Mean	SD
Birth week	38.54	2.88
Birth weight (grams)	3100.24	699.308
Exlusive breastfeeding (month)	4.09	2.51
Total breastfeeding duration (month)	17.17	10.97
Formula feeding duration (month)	12.89	7.13
Complementary feeding time (month)	6.0	0.6

SD: Standard deviation

In the measurements of the participants in 2021, the mean weight was 23.31±5.68 (min=12.5; max=41.7), weight SDS was 0.54±1.47, height mean. 117±5.67 (min=101; max=136), height SDS 048, and BMI mean 16.7±3.2 (min=11.75; max=29.17).

The average height was 117.74 cm, the average weight was 23.24 kg, and the body fat ratio was 21%. The mean BMI in 2021 was significantly higher than that in 2019 (t=47.24; p<0.001). The BMI changes of children by years are presented in. In addition, Table 5 presents the chi-square analysis of the BMI measurements in 2019 and 2021.

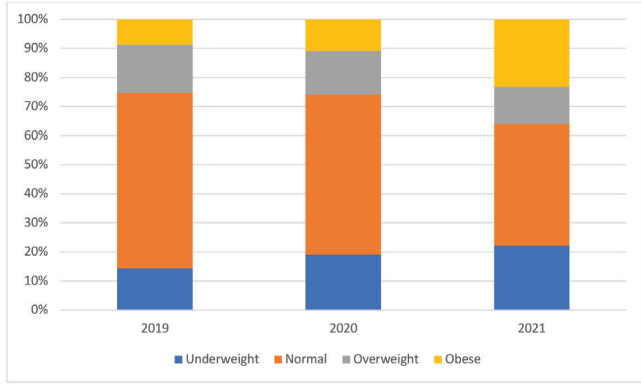
Table 3. Daily diet routines and activity habits of the children

		n*	%
Daily eating three main meals	Yes	147	77.0
	No	44	23.0
Regular packaged food consumption	Everyday	90	50.3
	1-3 days a week	89	49.7
Regular pastry consumption	Everyday	86	47.5
	1-3 days a week	92	50.8
Regular use of vitamin supplements	Everyday	6	3.1
	Nothing	179	92.3
Time spent in the playground	Days a week	140	72.2
	Nothing	54	24.8
Daily television watching time	3 hours and more	50	25.8
	Nothing	20	10.3
Daily tablet/phone using time	3 hours and more	85	43.8
	Nothing	24	12.4

*: Those who gave full answers to the questions were included in the analysis

Discussion

In the last measurements of the children participating in the study, their average height was 117.74 cm, their average weight was 23.24 kg, and their body fat percentage was 21%. Compared with 2019 measurements, our study showed that the overweight/obesity frequency statistically increased from 2019 to 2021. We also found that father's low



Graphic 1. Distribution of child participants based on BMI classificiation

BMI: Body mass index

Table 4. Some characteristics of the participants regarding their BMI measurements

		Normal BMI* n=121 (%)	High BMI** n=70 (%)	p	χ^2
Gender	Female	64 (60.4)	42 (67.1)	0.341	0.91
	Male	57 (39.6)	28 (32.9)		
Income status	Income less than expense	72 (62.6)	43 (37.4)	0.390	1.88
	Income equal to the expense	49 (65.3)	26 (34.7)		
Father has a university degree or higher	Yes	29 (80.6)	7 (19.4)	0.016	5.78
	No	92 (59.4)	63 (40.6)		
Daily eating three main meals	Yes	85 (70.2)	62 (88.6)	0.004	8.30
	No	36 (29.8)	8 (11.4)		
Regular packaged food consumption	Yes	110 (90.9)	69 (98.6)	0.034	4.47
	No	11 (9.1)	1 (1.4)		

*: Normal BMI and low BMI children are grouped as normal BMI, **: Overweight and obese children are grouped as high BMI, BMI: Body mass index

Table 5. BMI changes between 2019 and 2021

	2021 normal BMI and low BMI in	High BMI in 2021	Total
2019 normal BMI and low BMI in	110 (91.7)	32 (45.1)	141 (74.2)
2019 normal BMI and low BMI in	10 (8.3)	39 (54.9)	49 (25.8)
Total	120 (100)	71 (100)	191 (100)

χ^2: 50.78 p<0.001, BMI: Body mass index

educational level, eating 3 main meals, and more frequent consumption of packaged food were predictors for being overweight or obese.

As a result of the measurements in our research, 23.3% of 6-year-old children were obese. This indicates that our country may already pass the estimation of the World Obesity Federation which declared the prediction of percentage children aged 5-9 with obesity will be 22.9% by 2030 (9). This disturbing situation clearly reveals the effects of the pandemic on childhood obesity.

Our study results are in the same line with previous reports. A study from Korea showed that during the first year of the pandemic, the BMI of preschool and school-aged children increased significantly. Obesity frequency was risen to 18.6% from 14.6% and overweight frequency to 12.8% from 9.3% (10). Another study reported similar results. Among 2000 Indian children, the post-lockdown frequency of obesity was 7.8% and overweight was 17.8%; respectively, they were 5.4% and 13.8% pre-lockdown (11). A study conducted in Turkey revealed the effect of the pandemic among primary school students and demonstrated an increase in the frequency of obese students from 3.4% to 13.8% (12).

Ecological factors, such as social distancing, fewer physical activity options, and obesogenic environments; and biological factors like chronic stress and decreased immune function, were suggested as causes of obesity and COVID-19 collisions (13). Factors like lack of in-person contact with classmates, friends, and teachers; feelings such as frustration and boredom; and a potential lack of personal space at home may worsen the childhood obesity epidemic. Adverse childhood events resulting from a major increase in domestic violence during the pandemic are likely to have a considerable impact on childhood obesity and eating disorders in the future (14). Therefore, the pandemic's huge effect on childhood obesity should not be overlooked, and appropriate interventions must be implemented before it causes further damage.

Previous studies have shown that low parent education was associated with higher BMI and odds of overweight and obesity in children (7-11,15-19). Our results were partly coherent with those reports because we only revealed a significant relationship between paternal education and childhood obesity. Through their behaviors, parenting methods, and roles in defining the shared family environment of diet and physical exercise, both parents' educational levels are linked to their children's weight status and lifestyle. Furthermore, increased parental education may enhance family income, enabling more educated parents to access material resources more easily and effectively (19). Hence, public health interventions targeting parents with low education levels should be considered to prevent childhood obesity.

Depending on the mode of birth, the microbial composition of the infant's gut may affect the risk of obesity and metabolic disorders (20). Most previous studies reported that cesarean section may increase the risk of both overweight and obesity in children (21-23) although some suggested that there are no significant relationships (24,25). Similarly, our analysis did not reveal any differences between the delivery modes.

Previous studies have revealed a link between childhood obesity with metabolic comorbidities and parental obesity (26,27). In one study, the obesity rate of children whose parents were obese was reported to be 32.5% (20). It has been reported that environmental-gene interactions might play a major role in the consequences of parental obesity on offspring's body fat gain (28). However, we were not able to identify any relationship between maternal and paternal overweight/obesity and overweight/obesity in children.

Study Limitations

The main strength of our study is that we can generalize our results to all children in İstanbul because we selected the appropriate sample using scientific methods. Therefore, our results provide an accurate perspective on childhood obesity in children aged 6 years old. An important limitation of the study is that we measured the number of children only in 2021; we obtained data for 2019 and 2020 from the Ministry of Health database. In addition, five people were excludeed in the study because they moved to another city.

Conclusion

We were able to show an increase in childhood obesity among six-year-old children in İstanbul during the pandemic. Considering that the probability of the occurrence of pandemics and disasters will increase in the coming years, public health interventions, such as applications to increase children's physical activity, should be planned and prepared to prevent the increase in childhood obesity during these periods.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2000) and

was approved by the Ethics Committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey (2021.04.131).

Informed Consent: All participants provided informed consent.

Footnotes

Authorship Contributions

Concept: P.Ş.E., P.E.T., A.E.G., Design: P.Ş.E., P.E.T., A.E.G., Data Collection or Processing: P.Ş.E., Analysis or Interpretation: P.Ş.E., P.E.T., A.E.G., Drafting Manuscript: P.Ş.E., P.E.T., Critical Revision of Manuscript: P.Ş.E., P.E.T., A.E.G., Final Approval and Accountability: P.Ş.E., P.E.T., A.E.G., Writing: P.Ş.E., P.E.T., A.E.G.

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ORIGINAL RESEARCH

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Investigation of the Relationship Between Perceived Expressed Emotion and Levels of Impairment in Functioning Among Adolescents with Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Tanısı Olan Ergenlerin Algıladıkları Duygu Dışavurumu ile İşlevsellikte Bozulma Düzeyleri Arasındaki İlişkinin İncelemesi

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Abstract

Objective: To assess the perceived expressed emotion (EE) by adolescents with attention deficit hyperactivity disorder (ADHD) from their parents and to investigate the relationship between EE and impairment in functioning, as well as the relationship between internalizing and externalizing symptoms.

Method: The study population comprised 50 adolescents aged 12-17 years who had been diagnosed with ADHD. The adolescents were administered the shortened level of expressed emotion scale in adolescents (SLEES) and youth self-report (YSR) for the young people aged 11-18. The parents completed the Weiss functional impairment rating scale-parent form (WFIRS-P) and the child behavior checklist (CBCL) for children aged 6-18.

Results: It was found that there was a significantly higher difference in the subscale of maternal intrusiveness perceived by adolescents in males. The total score of perceived father's EE were found to be significantly different, which was higher in males ($p<0.05$). No statistically significant relationship was found between the total WFIRS-P score and the mother or father of SLEES. There was no statistically significant relationship between adolescents' perceived EE from their parents and the total internalizing and externalizing scores of the YSR. There was no statistically significant relationship between the adolescents' perceived EE from their parents and the total internalizing and externalizing CBCL scores.

Öz

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan ergenlerde ebeveynlerinden algıladıkları duygu dışavurumunu (DD) değerlendirmek ve DD ile işlevsellikte bozulma arasındaki ilişkiyi, içe yönelim ve dışa yönelim belirtileri arasındaki ilişkiyi incelemektir.

Yöntem: Çalışmaya DEHB tanısı konmuş 12-17 yaş aralığında 50 ergen dahil edilmiştir. Ergenlere ergenlerde kısaltılmış duygu dışavurum ölçeği (KDDÖ) ve 11-18 yaş gençler için kendini değerlendirme ölçeği (YSR) uygulanmıştır. Ebeveynlere Weiss işlevsellikte bozulma ölçeği-ebeveyn formu (WİBÖ-E) ve 6-18 yaş çocuklar için davranış değerlendirme ölçeği (CBCL) doldurulmuştur.

Bulgular: Erkeklerde müdahalecilik alanında annelerinde algıladıkları duygu dışavurum algısının daha yüksek olduğu saptanmıştır. Erkeklerin babalarında algıladıkları toplam duygu dışavurum algısının daha yüksek olduğu bulunmuştur ($p<0.05$). WİBÖ-E toplam puanı ile KDDÖ anne ve baba arasında anlamlı bir ilişki bulunmamıştır. Ergenlerin DD algıları ile kendilerini değerlendirdikleri YSR toplam, içe yönelim ve dışa yönelim puanları açısından istatistiksel olarak anlamlı ilişki saptanmamıştır. Ergenlerin algıladıkları DD'ler ile CBCL'nin toplam, içe yönelim ve dışa yönelim puanları arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır.

Sonuç: DD ile ilgili çalışmaların sonuçları, ebeveyn eleştirisinin ve çocukla düşük düzeyde olumlu ilişkinin DEHB belirtilerindeki değişimi

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Abstract

Conclusion: The results of studies on EE are inconclusive with regard to the question of whether parental criticism and low levels of positive relationships with children can predict changes in ADHD symptoms and whether they are potential predictors of changes in ADHD symptoms. Our findings indicated that despite the perceived high emotional expression of adolescents with ADHD, there was no significant relationship between perceived EE and functioning in daily life. Furthermore, our results demonstrated that the comorbidity of ODD in addition to ADHD did not lead to a significant difference in perceived EE.

Keywords: Adolescent psychiatry, attention deficit hyperactivity disorder, functional impairment, parents, perceived expressed emotion

Öz

yordayıp yordamadığı ve DEHB belirtilerindeki değişimin potansiyel yordayıcıları olup olmadığı sorusu açısından yetersizdir. Bulgularımız, DEHB'li ergenlerde algılanan yüksek duygu dışavuruma rağmen, algılanan DD ile günlük yaşamdaki işlevsellik arasında anlamlı bir ilişki olmadığını göstermiştir. Ayrıca, sonuçlarımız DEHB'ye ek olarak KOKGB komorbiditesinin algılanan DD'de anlamlı bir farklılığa yol açmadığını göstermiştir.

Anahtar kelimeler: Adölesan psikiyatri, algılanan duygu dışavurumu, dikkat eksikliği hiperaktivite bozukluğu, ebeveynler, işlevsellikte bozulma

Introduction

Attention deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder characterized by age-inappropriate inattention, hyperactivity, and impulsivity, which can adversely affect activities related to the community, school, or work (1). It has been reported that ADHD affects 5-7% of children worldwide (2). It is a well-established fact that oppositional defiant disorder (ODD), which is one of the most common categories of disruptive behavior associated with ADHD, has a high prevalence rate of 33% in adolescents (3). The available evidence indicates that the co-occurrence of an ODD diagnosis in conjunction with ADHD is associated with an elevated probability of problematic behavior, which in turn is associated with greater symptom severity and an increased risk of social difficulties (4).

It has been proven that parenting methods, psychopathologies, home stress, and parent-child conflicts affect ADHD symptoms, course, and outcomes (5). Expressed emotion was defined as a measure of parents' attitudes toward their children, such as hostilities, overinvolvement, critical comments and overprotectiveness/protectiveness (6). It has been hypothesized that expressed emotion, such as the expression of high levels of negative and low levels of positive emotions toward the child in parental attitudes, indicated family stress, poor quality parental support, and a negative parent-child relationship, which in turn affected the developmental course of the disorder, including an increase in ADHD symptoms and concomitant development of ODD, which may affect the recurrence and course of diseases (7-9).

In addition to revealing the interpersonal relationship, EE allows us to interpret children's daily functioning by measuring the quality of parents' behavior toward their children (10).

Parental EE may have concurrent and longitudinal associations with internalizing and externalizing problems and functioning in children and adolescents in community and clinical samples (11,12).

In addition, to screen for primary symptoms, assessment of EE and functional impairment at home and school is a critical aspect of the diagnosis and treatment of childhood ADHD. These factors play an important role in children's overall development and should be considered comprehensively (13).

This study aimed to investigate the perceived parental EE of adolescents who were diagnosed with ADHD with/without ODD and to examine the relationship between EE and the functional impairment of adolescents based on the statements of their families. Another objective of this study was to evaluate the internalizing and externalizing behaviors observed by adolescents in themselves and by their parents and the relationship between EE and these behaviors.

Materials and Methods

Participants

This study was conducted at the Kocaeli University Faculty of Medicine and received ethics committee approval from the Kocaeli University Faculty of Medicine Clinical Research Ethics Committee (project no: 2016/241). This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration. The study was conducted between March and September 2016 with 50 adolescent patients aged 12-17 years who were diagnosed with ADHD and/or ODD according to the semi-structured childhood schedule for affective disorders and schizophrenia-present and lifetime version-Turkish adaptation based on the diagnostic and statistical manual of mental disorders-5 diagnostic

criteria. Informed consent was obtained from the families of all patients who agreed to participate in the study.

Inclusion criteria: a) Diagnosis of ADHD or ADHD+ODD, b) aged 12-17 years, c) scoring above 80 on the Wechsler intelligence scale for children-revised (WISC-R) test, d) to have fully completed the scales in the study, e) living with at least one parent.

The exclusion criteria were as follows: a) Aged <12 years and/or >17 years, b) scored below 80 on the WISC-R test, c) chronic organic disease, d) diagnosed with conditions such as autism, anxiety disorder, schizophrenia, bipolar disorder, and psychotic disorder and general developmental delay, e) receive special education support, f) neurological disease, g) did not complete the scales in the study.

Materials and Methods

Socio-demographic information prepared by the researcher. Shortened level of expressed emotion scale in adolescents (SLEES) and the youth self-report for the young people aged 11-18 (YSR/11-18) were administered to the adolescents. Parents were asked to complete the weiss functional impairment rating scale-parent form (WFIRS-P) and the child behavior checklist for children aged 6-18 (CBCL/6-18). The CBCL was administered to evaluate the assessments of parents about behavioral and emotional problems in adolescents, and the YSR was administered to enable adolescents to self-report their emotional and behavioral problems. Accordingly, an objective mutual evaluation was planned.

Socio-demographic Data Form

The socio-demographic data form was developed by the authors to collect information pertaining to the socio-demographic characteristics of adolescents and their families. The form includes a series of questions regarding family information, including age, gender, educational status, parents' age and educational status, as well as the presence of mental and physical illnesses.

CBCL/6-18

CBCL assesses behavioral and emotional problems in children aged 6-18 years based on information provided by parents and was developed by Achenbach and tested for reliability in Turkey in 1985. The CBCL lists behavioral problems in two subtitles: "Internalizing problems" includes the "anxious/depressed, withdrawn/depressed, and somatic complaints" subtests and "externalizing problems" includes the "delinquent behaviors and aggressive behaviors" subtests (14,15).

YSR/11-18

The YSR assesses emotional and behavioral problems of children aged 11-18 years based on information they provide and was developed by Achenbach. The YSR classifies behavioral problems as follows: "Internalizing" and "externalizing". The internalizing group includes "anxious/depressed, withdrawn/depressed, and somatic complaints" and the externalizing group "delinquent behaviors and aggressive behaviors" subtests (16,17).

WFIRS-P

It is a 50-item Likert-type scale developed by Dr. Margaret Weiss to assess functional impairment associated with ADHD (18). Tarakçıoğlu et al. (19) conducted a validity and reliability study of the scale in Turkey. This includes the subheadings of family, school, life skills, child self-concept, social activities, and risky activities.

SLEES

SLEES was developed by Nelis et al. (20) and was adapted to Turkish by Vural et al. (21). The scale consists of 33 items that measure the EE of the most influential person in the participant's life in the last three months and involves the subscales of lack of emotional support (LES), irritability, and intrusiveness. High scores indicate a high degree of EE. The scale is read and filled out by the adolescent. A request was made by adolescents to provide a description of the emotional expressions they perceived from their parents, which they were to do by thinking about their parents (21).

Statistical Analysis

The data were analyzed using SPSS for Windows, 20.0 (IBM Corp, Armonk, NY, USA). The variables (numerical data) were tested for normality using the Kolmogorov-Smirnov test. Numerical variables with normal distribution are presented as mean +/- standard deviation. For normally distributed numerical variables, the difference between the groups was determined using the independent sample t-test. Differences between groups for numerical variables with non-normal distribution were determined using the Mann-Whitney U test and Kruskal-Wallis test. The relationships between numerical variables were evaluated using the Spearman Correlation Analysis. Statistical significance was set as $p<0.05$.

Results

In the study, 13 (26%) of the 50 patients were female, and 37 (74%) were male. The average age of the patient group was 13.7±1.69 years, ranging between 12 and 17 years. Of the patients in the study, 34 (68%) were primary school students and 16 (32%) were high school students.

The mean ages of the mothers of the adolescents was found to be 40.92±5.09, and 44.44±6.09 for the fathers. A total of 22 (44%) of the mothers of the adolescents had completed primary school, 9 (18%) had completed secondary school, 13 (26%) had completed high school, and 6 (12%) had completed university. Additionally, it was determined that 15 (30%) of the fathers of the adolescents had completed primary school, 9 (18%) had completed secondary school, 14 (28%) had completed high school, and 12 (24%) had completed university. The mothers of 17 patients (34%) and the fathers of 44 patients (88%) were engaged in either full-time or part-time employment. Among the families participating in the study, 22 (44%) had a physical disease. Moreover, 29 (58%) were found to have a mental disorder. A total of four patients presented for the first time, and 46 were under treatment. The diagnosis, ADHD subtypes, and treatment status of the adolescents are presented in Table 1.

The scores for the total and subscales of the SLEES are presented in Table 2. Given the possibility that perceived EE may vary according to sex, an analysis was conducted to determine whether such differences exist. The difference between the total and subscale scores of the perceived EE by adolescents according to sex is presented in Table 3. The subscale of maternal intrusiveness perceived by adolescents and the total score of perceived father's EE were found to be significantly different, which was higher in males ($p<0.05$).

The relationships between WFIRS-P and SLEES are presented in Table 4. No statistically significant relationship was identified between the WFIRS-P total score and SLEES mother and father ($p>0.05$). No statistically significant relationship was identified between the perceived EEs of adolescents and the total, internalizing, and externalizing scores of the YSR. Similarly, no statistically significant relationship was observed between the perceived EEs of adolescents and the total, internalizing, and externalizing scores of the CBCL. The relationships between the perceived EEs of adolescents and their CBCL and YSR scores are presented in Table 5.

Furthermore, an analysis was conducted to compare ADHD and ADHD+ODD comorbidity, ADHD subtypes, and gender with functioning, with the objective of determining whether such differences exist. No statistically significant difference was found between ADHD and ADHD+ODD and perceived EE. Similarly, no statistically significant difference was found between the subtypes of ADHD and perceived EE ($p>0.05$). The comparison of the total WFIR-S score according to sex, diagnosis, and ADHD subtype is presented in Table 6.

Table 1. Diagnosis, ADHD subtypes, and treatment status of the adolescents

Features	Groups	Number (n)	Percentage (%)
Diagnosis	ADHD	24	48
	ADHD+ODD	26	52
ADHD subtypes	ADHD-AD	20	40
	ADHD-HI	2	4
	ADHD-C	28	56
Treatment	No	4	8
	Yes	46	92

AD: Attention deficiency, ADHD: Attention deficit hyperactivity disorder, C: Combined, HI: Hyperactive/impulsive, ODD: Oppositional deficiency disorder

Table 2. SLEES total and subscale scores

SLEES scores	Mean ± SD
Maternal LES	48.24±7.91
Maternal irritability	20.84±7.57
Maternal intrusiveness	13.82±3.87
Maternal total score	82.90±9.28
Paternal LES	44.74±12.83
Paternal irritability	20.24±7.20
Paternal intrusiveness	12.46±3.85
Paternal total score	77.44±15.71

SD: Standard deviation, SLEES: Shortened level of expressed emotion scale, LES: Lacking emotional support

Table 3. Comparison of the SLEES total and subscale scores by sex

SLEES scores	Sex	Mean ± SD	Median	p
Maternal LES	Female	49.08±8.56	52	0.499
	Male	47.95±7.77	50	
Maternal irritability	Female	17.77±4.26	17	0.165
	Male	21.92±8.21	18	
Maternal intrusiveness	Female	11.69±2.42	12	0.016*
	Male	14.57±4.03	15	
Maternal total score	Female	78.54±8.26	80	0.132
	Male	84.43±9.23	84	
Paternal LES	Female	38.38±17.27	46	0.111
	Male	46.97±10.24	49	
Paternal irritability	Female	16.85±6.23	18	0.140
	Male	21.43±7.22	20	
Paternal intrusiveness	Female	10.69±4.44	12	0.119
	Male	13.08±3.47	13	
Paternal total score	Female	65.92±24.36	69	0.011*
	Male	81.49±8.57	79	

SD: Standard deviation, SLEES: Shortened level of expressed emotion scale, *: Mann-Whitney U test

Table 4. Relationship between WFIRS-P and SLEES

	SLEES		WFIRS-P total
Spearman's rho	Maternal total SLEES score	Correlation coefficient	-0.070
		Sig. (2-tailed)	0.629
	Paternal total SLEES score	Correlation coefficient	0.091
		Sig. (2-tailed)	0.530

SLEES: Shortened level of expressed emotion scale, WFIRS-P: Weiss functional impairment rating scale-parent report

Table 5. Relationship between SLEES, CBCL, and YSR scores

			YSR_I	YSR_E	YSR_T	CBLC_I	CBLC_E	CBLC_T
Spearman's rho	Maternal total SLEES score	Correlation coefficient	-0.017	-0.153	-0.016	-0.102	-0.111	-0.104
		Sig. (2-tailed)	0.909	0.289	0.914	0.481	0.443	0.471
	Paternal total SLEES score	correlation Coefficient	0.055	-0.108	-0.033	0.031	0.108	0.107
		Sig. (2-tailed)	0.706	0.454	0.822	0.833	0.457	0.458

CBLC_E: Child behavior checklist _ Externalizing, CBLC_I: Child behavior checklist _ Internalizing, CBLC_T: Child behavior checklist _ Total, YSR_E: Youth self-report _ externalizing, YSR_I: Youth self-report _ Internalizing; YSR_T: Youth self-report total

Table 6. Comparison of total WFIRS-P scores according to sex, diagnosis, and ADHD subtypes

Features		Weiss total score		
		Mean ± SD	Median	p
Sex	Female	21.62±14.85	17	0.682*
	Male	24.49±18.24	20	
Diagnosis	ADHD	20.04±13.45	17.50	0.180*
	ADHD+ODD	27.15±23.50	19.91	
ADHD subtypes	AD	21.50±16.08	18	0.640**
	HI	28.50±17.67	28.50	
	C	25±18.54	24	

*: Mann-Whitney U test, **: Kruskal-Wallis test, AD: Attention deficiency, ADHD: Attention deficit–Hyperactivity disorder, C: Combined, HI: Hyperactive/impulsive, ODD: Oppositional defiant disorder, SD: Standard deviation, WFIRS-P: Weiss Functional impairment rating scale-parent report

Discussion

This study examined the relationship between the perceived parental EEs of adolescents diagnosed with ADHD with/without ODD and the levels of impairment in functioning assessed by their families. A review of the literature revealed no studies that have evaluated the perceived parental EEs and impairment in functioning in patients with ADHD. Furthermore, studies in the literature on perceived EEs in adolescents with ADHD have been examined in terms of maternal EEs; however, this study analyzed the perceived EEs of both parents.

There is mounting evidence to suggest that there is a significant correlation between parenting skills and children's academic, social, and neuropsychological development (5,22). It has been reported that perceptions of children about their parents regarding their expressed behaviors due to ADHD may positively or adversely affect the quality of the parent-child relationship. Consequently, the comments made by parents may either enhance or diminish the influence of ADHD symptoms on the parent-child relationships (23).

No significant correlation was found between functional impairment and perceived parental EE in adolescents with ADHD. This result contradicts expectations. The fact that the treatment group constituted the majority of patients in our study and that the total WFIRS-P score was low in comparison with the literature suggests that EE may have been positively affected (24). The majority of patients attended regular follow-up visits, which may have facilitated the implementation of behavioral approaches to ADHD. However, to more accurately assess the relationship between the functioning of adolescents with ADHD and perceived parental EE, it may be beneficial to work with samples who have not received any medical or behavioral treatment and to include familial, environmental, and biological factors that may influence it. Impulsive reactivity, poor social skills, poor problem-solving ability, and social isolation, which are among the difficulties in the social functioning of adolescents with ADHD, may also cause family conflicts (25). The perception of high parental EE as a consequence of family conflict may have a detrimental impact on adolescents, thereby reinforcing the clinical symptoms of ADHD. Conversely, effective ADHD treatment may lead to a reduction in family conflict, which in turn may result in a decrease in parental EE.

The total score of perceived mother EE was 82.90±9.28, while the total score of perceived father EE was 77.44±15.71. In a further study by Ucar et al. (26), the total score for perceived EE was 63.2±15.3, with the following scores for the EE subscale: subscale of LES 28.8±9.7, subscale of irritability 19.9±6.7, and intrusiveness 14.4±3.2. A comparison of the present findings with those of previous studies indicates that perceived EE is higher in this context. The previous study was conducted according to the EE of individuals perceived as most important in the participant's life over the previous three months. Therefore, the present study may differ from the previous one due to the measurement of EE perceived by adolescents from their parents (26). A number of studies have indicated that mothers of children with ADHD are unable to fulfill their parental roles, communicate less with their children, and lack intimacy (27,28). Another study concluded that the majority of therapeutic interventions for EE currently in use are based on the assumption that maternal EE increases the likelihood of developing symptoms in adolescents (29). A review of the literature revealed no studies examining the correlation between perceived father EE by adolescents with ADHD. Given that mothers are typically housewives, they may have spent more time with their adolescents and may have experienced EE, protectiveness/overprotectiveness, and irritability more intensely. The finding that fathers were more likely to be employed outside the home suggests that they may have interacted less with their adolescents than mothers (30).

A comparison of total and subscale EE scores according to sex revealed a significant difference in the perception of maternal intrusiveness in males. The mother's perceived EE was higher in males. A review of the literature revealed no significant difference between female and male in the perceived parental EEs in children with ADHD (26). A study with a similar design to our own reached the same conclusion, namely, that mothers exhibit a more critical EE than fathers (31). The relationship between the maternal EEs toward males and the psychopathological symptoms of mothers and children was evaluated in a study by Psychogiou et al. (32), who found a positive relationship between criticism and ADHD symptoms and emotional and behavioral symptoms. The fact that males may have more age-specific expressive behaviors than females suggests that their perceived intrusiveness from their mothers, who are authority figures, may have increased.

The total perceived fathers EE scores were significantly higher among the male. It was reported that depressive symptoms of fathers had a more severe impact on males (33). Fathers of children with ADHD were determined to

be more demanding and assertive about power and were less likely to express warm feelings toward their children. It is possible that fathers react to the opposition of their sons by asking them to obey them rather than responding warmly (28,34). Fathers diagnosed with ADHD may have experienced discomfort or a sense of being overwhelmed by ADHD symptoms, which may have led to an increase in adverse parenting behaviors (32). Consequently, fathers may have focused excessively on and become overly interested in ADHD symptoms when their children with ADHD reached puberty. Consistent with previous research on the father-child relationship, our study found that adolescents with ADHD had less active interaction with their fathers, perceived less family support, and experienced more severe behavioral problems (34,35).

No significant differences were identified between ADHD and ADHD+ODD patients in terms of perceived parental EE. The results of our study are in line with those of a previous investigation conducted in Turkey (26). Sonuga-Barke et al. (36) reported that negative maternal EE concerning family and parent dynamics could potentially contribute to problematic behaviors and ODD in children with ADHD. The results of this study demonstrated that the EE was influenced by behavioral issues, maternal depression, and the range of additional mental health symptoms observed in children, rather than the symptoms of ADHD itself. In the six-year follow-up study conducted by Richards et al. (37), the cross-sectional and longitudinal relationships between behavioral problems in children with ADHD and parental EEs were examined. EE (maternal warmth and criticism) and the severity of ADHD symptoms were found to have a negative cross-sectional relationship with children's defiant, ODD, and conduct problems. However, a longitudinal analysis revealed no statistically significant correlation between the emotional state of the mother and subsequent manifestations of ODD/behavior disorder (DB) symptoms. In the study conducted by Richards et al. (38), a positive correlation was observed between maternal warmth, caregiving, and positive social behavior, while a negative correlation was noted between these same variables and antisocial behavior. Conversely, maternal criticism was found to be positively associated with antisocial behaviors. In our study, the exclusion of comorbid diseases, children with conduct problems were not included in the study, and the intensity of patients receiving treatment may have created a more naive patient sample group, which may have resulted in no discernible difference between the ADHD and ADHD+ODD groups.

It has been reported that impairment in family functioning is a significant factor in the development of ODD in children diagnosed with ADHD (39). The existing literature indicates that impairment in family functioning is more pronounced in children diagnosed with ADHD in the presence of comorbidities such as ODD (40). The findings of our study, however, revealed no significant difference in emotional expression, which is an important factor in family functioning, among families of adolescents with ADHD diagnosed with additional ODD. This finding is inconsistent with the literature.

The present study revealed no statistically significant difference in the perceived EE according to ADHD subtype. Ucar et al. (26) found that the perceived LES scores in the combined type of ADHD were higher than those in the attention deficit dominant type of ADHD. Çöp et al. (41) reported that children with ADHD, especially those with hyperactivity symptoms, considered their parents to be more indifferent, less affectionate, and more rejecting, and perceived them as less controlling. It should be noted that this study included adolescents who were under treatment and comprised a small sample group, which may have affected the results.

No significant relationship was found between the total, internalizing, and externalizing YSR scores and the perceived parental EE reported by the adolescents. Despite the limited data in the literature, high levels of perceived maternal EE are associated with high levels of internalizing and externalizing symptoms in adolescents (11,12). Another study reported no significant bidirectional relationship between parents' critical/positive comments and children's emotional problems (5). This is attributed to the fact that parents' responses to their children's emotional disorders may be less intense than those for behavioral disorders. According to the EE impact model theory, high EE family environments were believed to increase psychopathological distress in adolescents. However, our study results are inconsistent with these data, as no significant relationship was found between EE and adolescents' internalizing and externalizing evaluations. Furthermore, Hale et al.'s (42) six-year longitudinal study identified a psychopathological impact model that contradicted the common view that high EE family environments contribute to increased adolescent psychopathological distress. In our study, the positive outcomes of treatment in terms of functional internalization, externalization, and general symptoms positively influenced perceived EE, supporting Hale et al.'s (42) that expressive behaviors of adolescents may affect EE.

No significant relationship was found between the total, internalizing, and externalizing CBCL scores and the perceived parental EE reported by the adolescents. Despite the limited existing literature on the topic, evidence has suggested that high levels of maternal emotional expression are associated with elevated levels of both internalizing and externalizing symptoms in adolescents, as demonstrated by previous studies (11,12). The study conducted by Hale et al. (42) using the EE scale administered to mothers determined that the mothers' actions guided their EE, rather than the mothers' perceived EE affecting their behavior (43). In contrast, our study observed no relationship between the behavioral problems assessed by mothers and the adolescents' perceptions of parental EE. These findings suggest that improvements in children's functionality related to reduced behavioral difficulties may influence.

This cross-sectional study focused on adolescents with ADHD. However, to gain a more comprehensive understanding of the subject matter, it would be beneficial to conduct follow-up studies that encompass not only the adolescent period but also the early childhood, preschool, and school stages. It has been proposed that the inconsistency of the disparate study results on EE may be attributed to the inability to predict changes in EE over time, which is an image of a momentary situation susceptible to contextual and developmental factors. The argument has been made that perceived EE may be advantageous for understanding parental perceptions of their children in terms of their sensitivity to the developmental stages of children and early intervention in the EE (22,35).

Study Limitations

This study has some limitations. First, the small sample size precludes definitive conclusions. Second, there was a paucity of information on the mental health disorders of the parents. Third, the cross-sectional design makes it challenging to infer causality, and longitudinal studies are needed to address this.

The strengths of the study are the assessment of fathers' EE, which distinguishes from other studies. In addition, the YSR was completed by adolescents to assess psychiatric symptoms, and the CBCL was completed by parents to assess symptoms more reliably. It is recommended that a follow-up study with a larger sample size, including a control group, be conducted in the future to measure the confounding effect of intrafamilial EE on prognosis.

Conclusion

The results of studies on EE are inconclusive with regard to the question of whether parental criticism and low levels of positive relationships with children can predict changes in ADHD symptoms and whether they are potential predictors of changes in ADHD symptoms. Our findings indicated that despite the perceived high emotional expression of adolescents with ADHD, there was no significant relationship between perceived EE and functioning in daily life. Furthermore, our results demonstrated that the comorbidity of ODD in addition to ADHD did not lead to a significant difference in perceived EE. Furthermore, no significant difference was observed between emotional and behavioral internalizing and externalizing symptoms and EE. In our study, we concluded that ADHD, a neurodevelopmental disorder, did not significantly affect perceived expressed emotion, functioning in daily life, and emotional and behavioral internalizing and externalizing symptoms. This may indicate that children's perceived expressed emotion from their families, such as family stress or high protective attitudes, does not affect important areas in children''s lives.

Ethics

Ethics Committee Approval: Our study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine with decision number 2016/241 and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: We enrolled the patients after informing them about the study and obtaining their written consent.

Footnotes

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Authorship Contributions

Concept: Z.V.P., A.C., Design: Z.V.P., A.C., Data Collection or Processing: Z.V.P., Analysis or Interpretation: Z.V.P., A.C., İ.D.Ç., Drafting Manuscript: Z.V.P., A.C., İ.D.Ç., Critical Revision of Manuscript: Z.V.P., A.C., İ.D.Ç., Final Approval and Accountability: Z.V.P., A.C., İ.D.Ç., Technical or Material Support. Z.V.P., Supervision: Z.V.P., A.C., İ.D.Ç., Writing: Z.V.P., A.C., İ.D.Ç.

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ORIGINAL RESEARCH

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Evaluation of Serum Fibroblast Growth Factor 21 Levels in Gestational Diabetes Mellitus Patients

Gestasyonel Diabetes Mellituslu Gebelerde Serum Fibroblast Büyüme Faktör 21 Düzeylerinin Değerlendirilmesi

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Abstract

Objective: This study aimed to compare the clinical characteristics of pregnant women diagnosed with gestational diabetes mellitus (GDM) based on a 75-g oral glucose tolerance test (OGTT) with those of pregnant women who had normal test results and to evaluate the potential role of serum fibroblast growth factor-21 (FGF-21) levels in the diagnosis of GDM.

Method: This prospective, controlled cohort study a total of thirty-six pregnant women diagnosed with GDM based on a 75-g OGTT and thirty-six pregnant women with normal test results who presented to the Department of Obstetrics and Gynecology at University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital between 01/12/2021 and 01/04/2022 were included in the study. The participants' age and obstetric outcomes Neonatal characteristics, and laboratory results, including FGF-21 levels, were recorded.

Results: When the general characteristics of the participants in our study were evaluated, no statistically significant differences were found between the groups with and without gestational diabetes in terms of age, gravidity, parity, weight, birth weight, birth length, gestational week, hemoglobin, platelet count, and alanine transaminase and aspartate transaminase levels, indicating that the two groups were similar ($p<0.05$). However, when evaluated in terms of FGF-21 levels, a statistically significant difference was found between the group diagnosed with gestational diabetes and the group without it ($p<0.001$), with the group diagnosed with gestational diabetes had higher mean FGF-21 levels. No statistically significant relationship was found between FGF-21 levels and diet, medication use, or intensive care unit admissions ($p>0.05$). However, a statistically significant difference was found between FGF-21 levels and amniotic fluid index (AFI) increase ($p=0.003$). It was observed that

Öz

Amaç: Bu çalışmada 75 gr oral glikoz tolerans testi (OGTT) yapılarak gestasyonel diabetes mellitus (GDM) tanısı almış gebelerle ve test sonucu normal sınırlarda olan gebelerin klinik özelliklerinin karşılaştırılması, ve serum fibroblast büyüme faktörü-21 (FGF-21) düzeyinin GDM tanısında kullanılmasının yerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu çalışma prospektif, kontrollü kohort çalışması olarak planlanmıştır. 01/12/2021 ve 01/04/2022 tarihleri arasında Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne başvuran, 75 gr OGTT sonucuna göre GDM tanısı almış otuz altı gebe ve test sonucu normal sınırlarda olan otuz altı gebe çalışmaya dahil edilmiştir. Olguların yaşı, obstetrik sonuçları, yenidoğan özellikleri ve FGF-21'de dahil olmak üzere laboratuvar sonuçları kaydedilmiştir.

Bulgular: Çalışmamıza katılan kişilerin genel özellikleri gestasyonel diyabet olanlar ve olmayanlar açısından değerlendirildiğinde yaş, gravida, parite, kilo, doğum kilosu, doğum boyu, doğum haftası, hemoglobin, platelet, alanin transaminaz, aspartat transaminaz açısından istatistiksel olarak anlamlı bir fark saptanmadı ve iki grubun benzer özellik gösterdiği gözlendi ($p<0,05$). FGF-21 değerleri açısından değerlendirildiğinde ise gestasyonel diyabet tanısı alan grupla almayan grup arasında istatistiksel olarak anlamlı bir fark olduğu saptandı ($p<0,001$) ve gestasyonel diyabet olan grubun FGF-21 ortalama değerinin daha yüksek olduğu görüldü. Katılımcıların FGF-21 değerleri ile diyet, ilaç, yoğun bakım yatışı durumları incelendiğinde istatistiksel olarak anlamlı bir ilişki saptanmadı ($p>0,05$). FGF-21 değeri ile AFI artışı arasında ise istatistiksel olarak anlamlı bir fark saptandı. ($p=0,003$). Amniyon sıvısı indeksi (AFI) artışı olan kişilerde FGF-21 ortalama değerinin AFI normal olan gruba göre daha yüksek olduğu gözlendi.

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Abstract

participants with increased AFI had higher mean FGF-21 levels than those with normal AFI.

Conclusion: In this study, serum FGF-21 levels were higher in pregnant women with GDM than in those without GDM.

Keywords: FGF-21, Gestational diabetes mellitus, OGTT, pregnancy

Öz

Sonuç: Bu çalışmada GDM'li gebelerde serum FGF-21 düzeyi GDM olmayanlara göre daha yüksek bulundu.

Anahtar kelimeler: FGF-21, gebelik, gestasyonel diabetes mellitus, OGTT

Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance condition that begins or is diagnosed during pregnancy. Diabetes mellitus (DM) is not present before pregnancy but is diagnosed in the second or third trimester of pregnancy (1). The prevalence of GDM varies in direct proportion to the prevalence of type 2 diabetes. It is thought that 6-7% of pregnancies are complicated by DM, and approximately 90% of these are GDM (2).

Maternal tissues that provide adequate nutrition to the fetus throughout pregnancy become insensitive to insulin due to metabolic changes (3). One of these changes is that insulin-mediated glucose excretion decreases by 40-60% and an increase in insulin secretion of approximately 200-250% is required to maintain normal blood sugar levels (4). GDM occurs when a pregnant woman cannot produce enough insulin to compensate for this insulin resistance (4,5). Women diagnosed with GDM are at high risk for cesarean delivery and the development of preeclampsia. Additionally, women diagnosed with GDM have an increased risk of developing diabetes (usually type 2 DM) later in life (5,6).

GDM has negative effects on the fetus. Babies of women with GDM have an increased risk of birth trauma, shoulder dystocia, macrosomia, intrauterine growth restriction, fetal/neonatal hypertrophic cardiomyopathy, neonatal respiratory problems and metabolic complications, polyhydramnios, increased neonatal mortality and morbidity, risk of preterm birth, and respiratory distress syndrome (7-9).

The fibroblast growth factor (FGF-21) family comprises approximately 22 members. Their functions are generally related to angiogenesis, transformation, and mitosis. FGF-19, FGF-21, and FGF-23 have been proven to be endocrine factors (10). FGF-21 acts as an endocrine hormone. FGF-21 is produced by the liver, skeletal muscle, adipose tissue, pancreas, and placenta. It is an energy metabolism regulator that affects glucose and lipid metabolism (11). FGF-21 regulates glucose by increasing glucose uptake by adipocytes via glucose transporter-1 and decreasing blood glucose levels. This condition is independent of insulin (12). There is no interaction between FGF-21 and insulin during glucose reuptake. It has also been observed in animal experiments that FGF-21 inhibits glucagon release and lowers blood glucose levels (13). It has been observed that FGF-21 levels increase in insulin-resistant conditions such as Type 2 DM and obesity in humans (14). Some studies have shown that FGF-21 level has an independent diagnostic value for Type 2 DM (15,16).

Although the pathophysiology of GDM development remains unclear, the pathophysiology of GDM and Type 2 DM is believed to be similar. Insulin resistance and insulin insufficiency are caused by impaired pancreatic beta-cell function (1,8). For these reasons, whether a relationship similar to that between Type 2 DM and FGF-21 exists between GDM and FGF-21 is a subject for research. The aim of our study was to examine demographic characteristics by investigating the relationship between GDM and FGF-21.

Materials and Methods

This prospective, controlled cohort study was planned. In the power analysis, it was concluded that 22-25 patients were sufficient for the control and study groups. The study was terminated when 72 patients were reached within the target time. Of the patients who presented to the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Obstetrics and Gynecology Clinic between December 1, 2021, and April 1, 2022, the demographic, clinical, and laboratory values of thirty-six pregnant women who were diagnosed with GDM according to the 75-g OGTT result and thirty-six pregnant women whose test results were within normal limits were evaluated prospectively. Five patients were not included in the study because they had additional diseases. Three patients were excluded from the study because they were older than 40 years. GDM diagnosis was made in a single step as recommended by The International Association of the Diabetes and Pregnancy

Study Groups (17). Our study was conducted with the approval of Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (02.07.2021/43991-62/21).The study group consisted of pregnant women between 28 and 40 gestational weeks who were diagnosed with GDM and had no comorbidities. The control group consisted of healthy pregnant women who were not diagnosed with GDM and had no additional diseases. Because the patients were admitted to the hospital at 28-40 weeks of gestation after diagnosis, blood samples were collected at these weeks. Informed consent forms were obtained from all pregnant women included in the study. The patients were between the ages of 18 and 40 years and had singleton pregnancies. Pregnant women with genetic diseases, endocrine disorders, liver diseases, kidney failure, a history of diabetes, cardiovascular disease, or hypertension were not included in the study.

A total of 72 pregnant women met all criteria and were included in the study. Thirty-six people constituted the study group and thirty-six people constituted the control group. A 75-g OGTT was performed between 24 and 28 gestational weeks. According to the test results, patients were included in the study and control groups. Demographic data included age, gravidity, parity, fetal USG results, birth week, newborn weight, and need for intensive care were noted. Laboratory parameters and serum FGF-21 levels were noted.

Venous blood samples were placed in gel biochemistry tubes and centrifuged at 2000 rpm for 20 min. The serum samples were placed in an Eppendorf tube and frozen at 40 °C until analysis. When the analyses were to be performed, the samples were brought to room temperature. The collected serum samples were studied in a private laboratory using Microplate Reader RT 2100C and MicroplateWasher RT 2600C devices with human laminin enzyme kits. Serum FGF-21 concentrations were measured in pg/mL, and the reference range was determined as 1.6-100.

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, approved the study (02.07.2021/43991-62/21).

Statistical Analysis

In our study, version 21.0 of the SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) software was used for the statistical analysis of the data. In descriptive statistics, the mean, standard deviation, median, minimum, and maximum values were calculated for the variables.

As initial analyses, Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normal distribution. For comparisons between two groups, the Mann-Whitney U test was used for nonparametric data, and the t-test for independent groups was used for parametric data.

Spearman correlation analysis was used in the correlation analysis. In terms of correlation strength, r=0.00-0.24 was considered weak; r=0.25-0-49 was considered moderate; r=0.50-0.74 was considered strong; and r=0.75-1.00 was considered very strong.

The results were evaluated within the 95% confidence interval and $p<0.05$ was defined as statistically significant.

Results

Seventy-two pregnant women participated in the study. Gestational diabetes was diagnosed with OGTT in thirty-six of these pregnant women. The OGTT results of thirty-six pregnant women were normal, and they constituted the control group. When the general characteristics of the patients participating in our study were evaluated in terms of those with and without gestational diabetes, no statistically significant difference was detected in terms of age, gravidity, parity, weight, birth weight, birth length, birth week, hemoglobin, platelets, alanine transaminase (ALT), and aspartate transaminase (AST), and it was observed that the two groups showed similar characteristics ($p>0.05$) (Table 1). Regarding the FGF-21 values, a statistically significant difference was found between the group diagnosed with gestational diabetes and the group without ($p<0.001$) (Table 1). The mean FGF-21 level was higher in the group with gestational diabetes. Table 1 presents the general characteristics of the study participants for both the GDM and non-GDM groups.

When the participants in our study were evaluated in terms of those with and without gestational diabetes and their laboratory parameters were compared, no statistically significant difference was detected in terms of hemoglobin, platelet, ALT, and AST levels, and it was observed that the two groups showed similar characteristics ($p>0.05$) (Table 2).

The mean FGF-21 level was 26.7 pg/mL (11.5-110.8) in the GDM group and 17.2 pg/mL (11-28) in the control group (Figure 1). Compared with the control group, the FGF-21 level was significantly higher among GDM cases ($p<0.001$) (Figure 1).

As a result of the receiver operating characteristic analysis performed for the use of the FGF-21 level in the diagnosis of

GDM, the area under the curve was 0.838 (95% confidence interval: 0.746-0.930). When the FGF-21 cut-off value was selected as 22.75, the specificity value for the diagnosis of GDM was found to be 94.44%, sensitivity was 61.11%, positive predictive value was 91.7%, and negative predictive value was 70.8% (Figure 2).

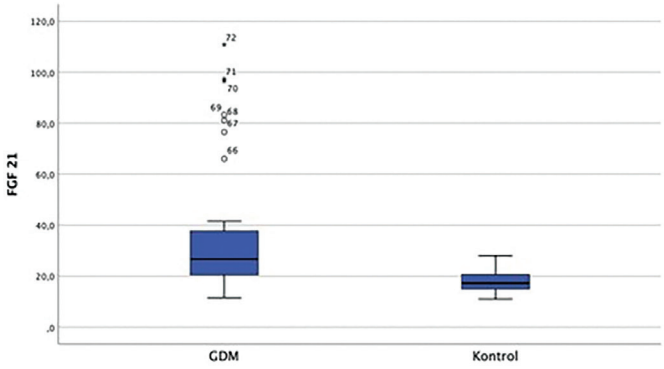

Figure 1. Graphical representation of the distribution of serum FGF-21 levels in the GDM and control groups

GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21

When the FGF-21 values of the participants and their diet, medication, and neonatal intensive care unit admission were examined, no statistically significant relationship was detected (p>0.05)(Table 3). A statistically significant difference was detected between the FGF-21 level and AFI increase (p=0.003) (Table 3). The mean FGF-21 level was higher in individuals with increased AFI than in those with normal AFI. The results are shown in Table 3.

Discussion

GDM causes serious maternal and fetal complications. Therefore, diagnosis and treatment are important. The most commonly used method is the oral glucose tolerance test. The American Diabetes Association and the International Association of Diabetes and Pregnancy Study Groups accept the one-step 75-g test. In a study conducted by

Table 1. Comparison of demographic characteristics between the GDM and non-GDM groups

	GDM	Non-GDM		Total
	Median (min-max)	Median (min-max)		Median (min-max)
	Mean ± SD	Mean ± SD	p	Mean ± SD
FGF-21	26.7 (11.5-110.8)	17.2 (11-28)	<0.001*	20.6 (11-110.8)
Age	34.5±5.86	31.3±4.57	0.198**	32.11±5.28
Gravidity	3 (1-8)	2 (1-5)	0.138*	3 (1-8)
Parity	2 (0-7)	1 (0-4)	0.430*	1 (0-7)
Kg	78.5±8.7	76±7.1	0.162**	77.4±7.97
Height	160.8±5.85	160.1±5.32	0.600**	160.4±5.56
Birth weight	3415±538	3220±570	0.139**	3318±559
Birth length	49.2±2.17	48.5±2.74	0.257**	48.9±2.48
Birth week	38.1±1.41	38.1±1.69	1**	38.1±1.53

*: Mann-Whitney U test result, **: t-test results, SD: Standard deviation, GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21

Table 2. Comparison of laboratory parameters between the GDM and non-GDM groups

	GDM	Non-GDM		Total
	Median (min-max)	Median (min-max)		Median (min-max)
	Mean ± SD	Mean ± SD	p	Mean ± SD
Hgb	11.6±0.97	11.9±1.37	0.194**	11.7±1.19
PLT	210±2±63.37	219.7±77.54	0.579**	214.8±70.23
ALT	12 (6-25)	9 (5-53)	0.065*	11 (5-53)
AST	16 (8-30)	17 (9-78)	0.316*	16.5 (8-78)
Urea	14±3.94	13.8±4.66	0.839**	13.9 ±4.27
Uric acid	3.4 (1.4-6.8)	3.7 (2.4-5.8)	0.328*	3.5 (1.4-6.8)
Creatinine	0.47 (0.34-0.79)	0.51 (0.37-0.77)	0.059*	0.48 (0.34-0.79)

*: Mann-Whitney U test result, **: t-test results, AST: Apartate transaminase, ALT: Alanine transaminase, SD: Standard deviation, GDM: Gestational diabetes mellitus, PLT: Platelet, Hgb: Hemoglobin

ElSayed et al. (18) in 2023, the importance of the 75-g OGTT approach was emphasized. Therefore, in our study, 75-g OGTT results were examined. Treatment of the diagnosed pregnant woman should be started immediately based on the test results. This treatment consists of diet, exercise, and medical treatment. Treatment should be decided by the clinician according to the patient's condition. Studies have shown that treatment initiation improves maternal and fetal outcomes. The main findings of our study are as follows. FGF-21 serum levels were found to be significantly higher in pregnant women diagnosed with GDM than in normal pregnant women without GDM diagnosis. A significant relationship was found between serum FGF-21 levels and AFI in pregnant women. No significant relationship was found between serum FGF-21 levels and fetal outcomes (birth weight, birth length, need for neonatal intensive care).

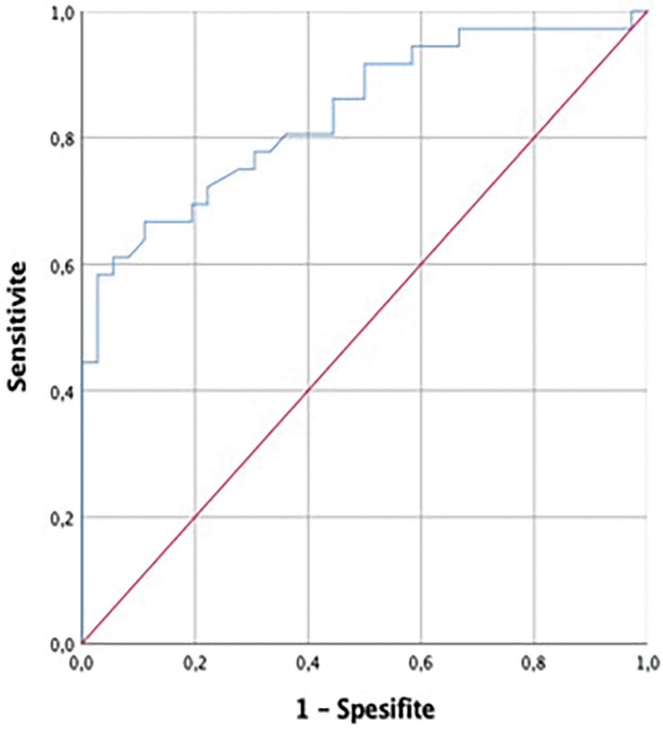

Figure 2. ROC curve showing the ability of FGF-21 level to distinguish GDM

GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21, ROC: Receiver operating characteristic

When the general characteristics of the people participating in our study were evaluated in terms of those with and without GDM, no statistically significant difference was detected in terms of age, gravidity, parity, weight, birth weight, birth length, birth week, hemoglobin, platelet, alanine aminotransferase, and aspartate aminotransferase, and the two groups were observed to have similar characteristics.

In our study, serum FGF-21 levels were found to be significantly higher in the GDM group than in the non-GDM group. In a study conducted in the Caucasus by Tan et al. (15), the relationship between GDM and FGF-21 was investigated. In the study conducted with a total of 24 patients 12 diagnosed with GDM and 12 in the control group, samples were collected before elective cesarean section between 39 and 40 weeks. FGF-21 was found to be significantly higher in the GDM group. High FGF-21 levels were found to be similar to those in our study (15). In the study conducted by Wang et al. (16) in China, with a control group of 60 people and 30 patients with GDM, samples were collected between 24-28 gestational weeks after OGTT. FGF-21 levels were found to be significantly higher. In our study, samples were collected between 28 and 40 gestational weeks. Similar to this study, serum FGF-21 levels were found to be significantly higher than those in the control group (16). In a study conducted in China by Li et al. (19) with a total of 101 patients 51 diagnosed with GDM and 50 in the control group, FGF-21 serum values

Table 3. Comparison of the effect of FGF-21 on maternal and fetal outcomes between the GDM and non-GDM groups

		FGF-21	
		Mean (min-max)	**p**
Medication use*	Yes	25.5 (15.9-110.8)	0.570
	No	28.2 (11.5-96.5)	
Diet*	Yes	28.2 (11.5-96.5)	0.570
	No	25.5 (15.9-110.8)	
AFI	Normal	18.8 (11-76.5)	0.003
	Increased	25.5 (12.6-110.8)	
Newborn intensive care unit admission	Yes	19.5 (11-110.8)	0.720
	No	20.8 (11.5-96.5)	

*: Only the GDM group, GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21, AFI: Amniotic fluid index

were compared between the GDM and non-GDM groups at the 28th gestational week and the 7th postpartum day. The serum FGF-21 level in the GDM group was significantly higher. A decrease in serum concentrations was observed in both groups. This indicates that studies can be conducted to determine whether the FGF-21 level in both patient groups may increase with conditions such as insulin resistance and carbohydrate intolerance during pregnancy and that it may return to normal after birth. The finding that FGF-21 levels are high during pregnancy is consistent with our study (19). No significant difference was found between FGF-21 levels in studies conducted by Dekker Nitert et al. (20) in Australia and Wang et al. (21) in China. However, the number of cases in these studies was limited to 45 and 38 patients. The higher number of cases in both our study and the other studies suggests that the results are stronger (20,21).

In our study, a significant relationship was found between AFI and FGF-21, but the relationship between them was not mentioned in previous studies. Our study revealed that this problem should be investigated in new studies.

In studies on GDM and fetal outcomes, when case and control groups are compared, a significant difference is detected in fetal outcomes and baby birth weight. Patients with GDM are more likely to experience macrosomia. In a study conducted by Kc et al. (22), a relationship was shown between macrosomic babies and GDM. In our study, when birth weight was compared, the average birth weight of the GDM group was 3415±538 g, and that of the control group was 3220±570 g. Although the average birth weight was higher in the GDM group, there was no significant difference between the two groups. The reason for this was thought to be the fact that the patients diagnosed with GDM in our study were monitored by gynecologists, obstetricians, and endocrinologists after diagnosis and were treated with diet, exercise, and medical treatment options.

In the GDM group, the treatment type (diet-medical treatment) and FGF-21 serum levels were compared. No correlation was found between elevated serum FGF-21 levels and planned treatment.

Since our study was a prospective study, all the parameters evaluated in the patients were collected completely. This feature was one of the strengths of our study. No significant differences were detected between the groups in terms of age, body mass index, gravidity, parity, and laboratory parameters. Pregnant women with genetic diseases, endocrine disorders, liver diseases, kidney failure, a history of diabetes, cardiovascular disease, or hypertension were not included in the study. This indicates that there is no difference between our case and control groups other than GDM, and that both groups have similar characteristics. The fact that the case and control groups had similar characteristics was another strength of our study.

Study Limitations

There are some limitations in our study. Blood samples were collected from the case and control groups. No opinions can be expressed on whether the results will be affected by repeated sampling. All samples were collected after performing the OGTT on the patient. This means that serum FGF-21 levels could not be compared with those obtained weeks before the diagnosis and prior to the OGTT. In addition to these, the fact that our study was single-centered was another limitation.

Conclusion

In conclusion, our study found that serum FGF-21 levels were significantly higher in the GDM group. This indicates that FGF-21 can be used as a GDM diagnostic test if supported by studies conducted in the coming years. This test can be used in the diagnosis of GDM in the following years in centers where OGTT cannot be performed or for patients who do not want to undergo testing by performing a glucose challenge. It may be easier and more accessible for patients to undergo testing. FGF-21 can be used in the diagnosis and treatment of GDM, but further studies are needed to understand whether this parameter can be used.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, approved the study (02.07.2021/43991-62/21).

Informed Consent: Informed consent forms were obtained from all pregnant women included in the study.

Footnotes

Authorship Contributions

Concept: N.Ç.Ç., H.Ö.Ç., V.M., Design: N.Ç.Ç., H.Ö.Ç., V.M., Data Collection or Processing: N.Ç.Ç., S.G., E.A., Analysis or Interpretation: N.Ç.Ç., H.Ö.Ç., Drafting Manuscript: N.Ç.Ç., H.Ö.Ç., S.G., Critical Revision of Manuscript: N.Ç.Ç., E.A., V.M., Final Approval and Accountability: N.Ç.Ç., H.Ö.Ç., E.A., S.G., V.M., Technical or Material Support: N.Ç.Ç.,

H.Ö.Ç., V.M., Supervision: N.Ç.Ç., S.G., E.A., Writing: N.Ç.Ç., H.Ö.Ç., E.A., S.G., V.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Is Decreased Serum AMH Level an Independent Risk Factor for Ectopic Pregnancy?

Düşük Serum AMH Seviyesi Ektopik Gebelik için Bağımsız Bir Risk Faktörü müdür?

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Abstract

Objective: The aim of this study was to investigate the possible relationship between the frequency of tubal ectopic pregnancy and serum anti-Mullerian hormone (AMH) levels.

Method: In this prospective study, a comparison is made between a group of 106 healthy women and a group of 106 women who were diagnosed with first-trimester tubal ectopic pregnancies through natural conception. Although no known reason for ectopic pregnancy was identified, patients diagnosed with ectopic pregnancy and hospitalized were included. The ectopic pregnancy group comprised women aged 22-43 years, and the control group comprised women aged 22-40 years. Women known to have low ovarian reserve were excluded, as were women with a family history of premature ovarian failure, and those with additional causes that may decrease ovarian reserve, such as pelvic surgery. In addition, cervical, heterotopic, ovarian, or ectopic pregnancies of unknown location were excluded from the study. Serial beta-human chorionic gonadotropin and transvaginal ultrasonography were used for the diagnosis of ectopic pregnancy, along with the measurement of serum AMH level as an indicator of ovarian reserve.

Results: In both groups, a lower serum AMH level was negatively correlated with increasing age (r=-0.210, p<0.01), and the ectopic pregnancy group had lower serum AMH levels (1.51 and 3.69 ng/mL, respectively, p<0.001) than healthy women of equivalent age. Ectopic pregnancy was found to increase 1.7 times with each 1-ng/mL decrease in AMH.

Conclusion: According to the results of the study, decreased serum AMH levels in women of all ages increased the frequency of ectopic pregnancy.

Keywords: Anti-Müllerian hormone, ectopic pregnancy, ovarian reserve

Öz

Amaç: Bu çalışmanın amacı, tubal ektopik gebelik sıklığı ile anti-Müllerian hormon (AMH) düzeyleri arasındaki olası ilişkiyi araştırmaktır.

Yöntem: Bu prospektif çalışmada, 106 sağlıklı kadından oluşan bir grup ile spontan ilk trimester tubal ektopik gebelik tanısı konan 106 kadından oluşan bir grup arasında bir karşılaştırma yapılmıştır. Ektopik gebelik için bilinen bir neden olmamasına rağmen, ektopik gebelik tanısı konan ve hastanede yatarak tedavi edilen hastalar dahil edilmiştir. Ektopik gebelik grubu 22 ila 43 yaşları arasındaki kadınlardan, kontrol grubu ise 22 ila 40 yaşları arasındaki kadınlardan oluşmuştur. over rezervi olduğu bilinen kadınlar, ailesinde prematüre over yetmezliği öyküsü olan kadınlar ve pelvik cerrahi gibi over rezervini azaltabilecek ek nedenleri olan kadınlar çalışma dışı bırakılmıştır. Ayrıca, servikal, heterotopik, ovarian gebelikler ve yeri bilinmeyen ektopik gebelikler çalışma dışı bırakılmıştır. Ektopik gebelik tanısı için seri beta-insan koryonik gonadotropin ve transvajinal ultrasonografi, over rezervi testi olarak da serum AMH değeri kullanılmıştır.

Bulgular: Her iki grupta da artan yaşla negatif korelasyon gösteren daha düşük serum AMH değeri bulduk (r=-0,210, p<0,01). Ektopik gebelik grubunun, aynı yaştaki sağlıklı kadınlara kıyasla daha düşük serum AMH düzeyi (sırasıyla 1,51 ve 3,69 ng/mL, p<0,001) olduğunu bulduk. AMH düzeyindeki her 1 ng/mL'lik düşüş ile ektopik gebelik 1,7 kat arttı.

Sonuç: Araştırmamız sonuçlarına göre doğurganlık çağındaki kadınlarda azalmış serum AMH düzeyleri ektopik gebelik oranını artırmaktadır.

Anahtar kelimeler: Anti-Müllerian hormon, ektopik gebelik, over rezervi

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Introduction

An ectopic pregnancy is a blastocyst implantation outside the endometrium. The incidence of ectopic pregnancy among all pregnancies is 12% (1). The mortality rate of ectopic pregnancy is 0.48 per 100,000 live birth (2).

Known risk factors for ectopic pregnancy include smoking, intrauterine device use, previous ectopic pregnancy, pelvic infection and surgery, and tube diseases. In addition, ectopic pregnancies in artificial reproductive technology (ART) pregnancies are observed 2.55 times more frequently than normal pregnancies (3,4).

The ovary and the endocrine environment it creates after ovulation affect the journey of the blastocyst and its attachment to the endometrium. A healthy ovary is therefore essential for the formation and continuation of pregnancy. The relationship between decreased ovarian function and ectopic pregnancy is not clear. Regardless of the embryo transfer technique, ectopic pregnancy develops more frequently than spontaneous pregnancies in women with decreased ovarian reserve who undergo ART. In fact, decreased ovarian reserve during ART cycles is considered an independent ectopic pregnancy risk factor (5).

Half of the women diagnosed with ectopic pregnancy had no risk factors (6). Both this situation and the increase in ectopic pregnancies in ART pregnancies, independent of the embryo transfer technique, … a relationship between the decrease in ovarian reserve and ectopic pregnancy.

To the best of our knowledge, no study has yet investigated the relationship between ectopic pregnancy risk and ovarian reserve in natural pregnancies. In this study, we aimed to investigate whether the frequency of ectopic pregnancy is associated with ovarian reserve in spontaneously pregnant women who have not received assisted reproductive technology or infertility treatment.

Materials and Methods

According to the Declaration of Helsinki, this prospective study was performed with the permission of the Clinical Research Ethics Committee of a İstanbul Medipol University (dated: 23.06.21, decision no: 731).

The study was initiated after obtaining detailed verbal and written consent from all participants, with approval from the ethics committee. The study was conducted with a total of 212 women at a gynecology and obstetrics clinic at a tertiary health center from June 2021 to October 2022.

By October 2022, 150 hospitalized patients with ectopic pregnancy were included. Heterotopic pregnancies, women with autoimmune diseases, women with a history of pelvic infection, women with a history of pelvic surgery, women diagnosed with polycystic ovary syndrome, women with primary ovarian insufficiency (POI) or diminished ovarian reserve (DOR), women who smoked, women with previous ectopic pregnancies, and those with non-tubal ectopic pregnancy were excluded from the study. Ten patients who voluntarily left the hospital after hospitalization and six patients aged >45 years and 21 years were excluded. Two patients diagnosed with ectopic and heterotopic pregnancy were excluded from the study. After hospitalization, 13 patients with known risk factors for ectopic pregnancy (intrauterine device use less than two months ago, pelvic surgery, pelvic infection, systemic lupus erythematosus, patients with thyroid disease, women who smoke regularly, patients with previous ectopic pregnancy, etc.) and two patients with pregnancy that occurred while receiving infertility treatment were excluded from the study; related data were not processed, and the study was performed with the data of the remaining 106 patients.

In the control group, 106 healthy women who applied to the gynecology and obstetrics clinic for control or with a complaint of vaginitis were planned. Women with menstrual irregularities, endocrine diseases, early menopause in the family, obesity, anorexia, and who smoked were excluded from the control group. Ten of the 120 women were excluded from the study because they did not undergo blood testing, and four of them disclosed that they smoked later.

Finally, a total of 106 ectopic pregnancy patients (diagnosed with tubal ectopic pregnancy in the first trimester and conceived naturally) aged between 22 and 43 years and 106 healthy women aged between 22 and 40 years (routine check-ups or complaints of vaginitis) were included in the study. Age, pregnancy, and additional disease history of the patients were recorded. Transvaginal ultrasonography (GE Logic 200 Pro, 5 MHz vaginal probe) was performed in all patients. Blood was collected from each patient to measure the beta-human chorionic gonadotropin (BHcg) and anti-Mullerian hormone (AMH) values and then studied without waiting. Serum AMH levels were measured using the Elica technique (Roche E411, USA).

Although the BHcg value was the pregnancy level, women whose intrauterine gestational sac could not be seen or who had a gestational sac in the tube on ultrasonography were recorded as having an ectopic pregnancy. Since reliable data could not be obtained via ultrasonography in women with very low BHcg values, serial BHcg tests were performed

first, and women who did not show an acceptable increase were included in the study group.

A detailed anamnesis was obtained from the patients in the control group during their first examination. Then, during gynecological examination, ultrasonography was performed, and blood was drawn for AMH.

Statistical Analysis

Mean standard deviation and median interquartile range values are given in descriptive statistics for continuous data, and the number and percentage values are given in discrete data. The Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution.

An independent samples t-test was used to compare patient ages with and without ectopic pregnancy, and the Mann-Whitney U test was used to compare AMH values between the two groups.

Multivariate logistic regression analysis was used to determine whether age and AMH were effective risk factors for ectopic pregnancy.

The IBM SPSS version 20 (Chicago, IL, USA) software was used in the evaluations and $p<0.05$ was considered statistically significant.

In a study in which 106 patients with ectopic pregnancies and 106 patients were included as the control group, and the AMH values were compared as the primary outcome, the power of the test was found to be d=0.98 (effect size), Type I error =0.05, and power =0.99 (99%). The calculation was performed using GPower 3.1.9.2 software.

Results

The study included 106 women diagnosed with ectopic pregnancy and 106 healthy women. The minimum age of patients with ectopic pregnancy was 22 years, and the maximum age was 43. The mean age of both groups was 32 years, and no statistically significant difference was found ($p>0.05$). The minimum and maximum age of patients with ectopic pregnancy patients was 22 and the maximum age was 43 (Table 1).

All patients in the control group had been pregnant at least once previously, whereas 88 women (83%) in the ectopic pregnancy group had been pregnant previously.

One-third (30%) of the ectopic pregnancy group required surgical treatment.

The AMH level in the study group was between 0.04 and 7.35 ng/mL; in the control group was between 0.76 and 14.90 ng/mL.

A significant difference was found between the AMH values of the ectopic pregnancy group and the control group (respectively 1.51, 3.69 ng/mL, $p<0.001$). The AMH value was lower in the ectopic pregnancy group than in the non-pregnant group (Table 1).

In patients aged ≤24 years, 2530 years, 3135 years, 3640 years, AMH values were lower than the thresholds in the literature (3 ng/mL, 2.5 ng/mL, 1.5 ng/mL, 1 ng/mL, 1 ng/mL and 0.5 ng/mL, respectively) (50%, 61%, 50%, 46%, respectively) (Table 1). All three of the patients aged ≥40 years had AMH values below 0.5 ng/mL.

Six of the women with low AMH were aged 2030 years, 15 were aged 3040 years, and seven were aged 40 and over. A negative correlation was observed between patient age and AMH values ($r=-0.210$, $p<0.01$). The AMH values decreased as the patient age increased (Table 2).

As a result of the multivariate logistic regression analysis, the AMH values were found to be an effective factor for

Table 1. Comparison of age and AMH values of patients with ectopic pregnancy and control patients gravida, previous pregnancy, surgical therapy features of patients with ectopic pregnancy

	Ectopic pregnancy	Control	p-value
Age (years) mean ± SD	31.96±5.20	31.74±4.05	0.724[a]
AMH median (IQR)	1.51 (0.842.86)	3.69 (2.1014.90)	<0.001[b]
Gravida median (IQR)	3 (24)	2 (13)	0.05

[a]: Independent samples ttest, [b]: Mann-Whitney U test, SD: Standard deviation, AMH: Anti-Müllerian hormone, IQR: Interquartile range

Table 2. Correlation between the ages of every patient (n=212) and AMH

	Age	
	r	p
AMH	-0.210	0.002

AMH: Anti-Müllerian hormone

Table 3. Multivariate logistic regression analysis for age and AMH values considered to be effective on ectopic pregnancy

Variable	Regression coefficient (SE)	OR	95% CI		p-value
Age	-0.041 (0.035)	1.041	0.972	1.114	0.244
AMH	-0.548 (0.095)	1.730	1.434	2.083	<0.001

AMH: Anti-Müllerian hormone, OR: Odds ratio, CI: Confidence interval

ectopic pregnancy (p<0.001). Each 1-ng/mL decrease in AMH increased ectopic pregnancy by 1.730-fold (Table 3).

Discussion

In this study, we compared the ovarian reserves of healthy women and those diagnosed with ectopic pregnancy at similar ages. We found that the ovarian reserve decreased with increasing age. However, we found that ovarian reserve was lower in our ectopic pregnancy group regardless of age.

The incidence of ectopic pregnancy increases with increasing female age. While the incidence is 3% in women aged 20 years, it reaches 10% in women aged >40 years (7). This increase in the incidence of ectopic pregnancy can be explained by increasing age, decreased ovarian reserve, use of contraception methods, cumulative increase in infection, endometriosis, adhesion, surgery, and treatment for infertility. Accumulation of chromosomal abnormalities in the oocytes of women of advanced age, cumulus cell dysfunctions, and consequent deterioration of oocyte quality and acceleration in apoptosis are also associated with an increased risk of ectopic pregnancy (8). Therefore, decreased ovarian reserve may be one of the most important underlying factors in young women presenting with ectopic pregnancy. The patients in our study were mostly young women, only nine of whom (10%) were aged 40 years or older.

Studies have shown that decreased ovarian reserve is associated with ectopic pregnancy. In these studies, conducted with ART cycles, serum follicle-stimulating hormone/estradiol (FSH/E2) level was generally used as an ovarian reserve test. In this study, we used serum AMH levels rather than FSH/E2 or the antral follicle count as the ovarian reserve test. Although gonadotropin levels and antral follicle count are generally used as ovarian reserve tests, they may not be useful in diagnosing ectopic pregnancy as hormone levels are not reliable in terms of ovarian reserve due to physiological hypogonadism during pregnancy, and the number of antral follicles may also not be optimal for reasons such as pregnancy mass and intra-abdominal collection.

AMH is a marker reflecting the primordial cell pool. In our study, the AMH level also decreased as the age of the patient increases. There may be intra- and inter-assay variability in AMH tests, but there is no international standard monogram. However, considering its advantages, such as low intra- and intercycle variability and ease of use, and not being greatly affected by the use of oral contraceptives and gonadotropins, it can be said that it is sufficient to be used alone in the evaluation of ovarian reserve (9). AMH levels are lower in pregnancy than in the non-pregnant period. Moreover, as the gestational age increases, AMH decreases even more and increases again after delivery. In the literature, it has been reported that the mean AMH level in the first trimester is 1.69 ng/mL (if measured by ELISA) (10). All patients in our study group were in the first trimester (<13 weeks), and we detected AMH levels below 1.69 ng/mL in 58 of our patients. We accepted 1 ng/mL as the low cut-off value for ovarian reserve (11). In our study, 21 of the patients with low AMH were older than 40 years, and one-third of our patients (28 patients) in the ectopic pregnancy group had AMH <1 ng/mL. In accordance with the literature, we found that AMH decreased with increasing age. In addition to this natural decrease, we found low AMH levels in our ectopic pregnancy group, even in young patients. Furthermore, we observed that the risk of ectopic pregnancy increased 1.7-fold with each 1-unit decrease in AMH (Table 2).

It has been shown that the incidence of ectopic pregnancy in women undergoing ART is 13 times higher than the incidence of ectopic pregnancy in natural contraception pregnancies (2.03.5% vs. 1.52.0%) (12). This increased risk is attributable to both the woman's medical condition requiring ART (age, tubal diseases, endometriosis, etc.) and the direct ART technique. Although it was thought that an embryo with anomalies could not achieve the tubal journey due to an increase in the rate of chromosomal anomalies in women of advanced age who underwent ART, this could not be proven (13-15).

The incidence of ectopic pregnancy was found to be higher in women with DOR who underwent ART, with the increased rate attributed to poor oocyte quality, decreased

implantation capacity in the blast formed by fertilization of the oocyte, and implantation before reaching the cavity. However, considering that the possibility of ectopic pregnancy increases in advanced stages of ART cycles, … this will also be associated with decreased ovarian reserve.

The increase in the rate of ectopic pregnancy in young patients with low AMH levels supports this hypothesis, whereas studies with ovarian reserve mostly used FSH. Studies conducted with women with high FSH levels have also shown a relationship between low ovarian reserve and ectopic pregnancy [Lin et al (5)]. When ART was performed on women with FSH >10 IU/L, which is accepted as a low ovarian reserve criterion, ectopic pregnancies were observed more frequently. When confounding factors were eliminated, the authors concluded that only decreased ovarian reserve increased the rate of ectopic pregnancy in ART pregnancies and reported that decreased ovarian reserve is an independent risk factor for ectopic pregnancy (5).

In this study, which included patients with natural ectopic pregnancies, we also found a significant decrease in AMH among women diagnosed with ectopic pregnancy. The fact that we found that the risk of ectopic pregnancy increased approximately two-fold with every one unit of AMH decrease indicates that there is a direct relationship between ovarian reserve and the risk of ectopic pregnancy.

The decrease in ovarian reserve and increase in the incidence of ectopic pregnancy may be related to many factors. In women with DOR, a lack of hormone effects that ensure optimal endometrial receptivity development during embryo transfer is also a factor. DOR may be an independent risk factor for IVF/ET cycles, which is in line with the results of previous publications for patients considered to have reduced ovarian reserve based on FSH levels alone. This is likely due to deterioration of oocyte quality. This leads to decreased embryo quality, a suboptimal hormonal environment, and subsequent implantation failure. If endocrine factors are supported with medications, an increase in the possibility of intrauterine pregnancy may indicate the importance of hormonal changes (12,16). These factors may increase the risk of ectopic pregnancy. In immunohistochemical examinations, βcatenin was strongly expressed in tubal implantation sites in ectopic pregnancies following IVFET compared with non-pregnant tubal tissues. βcatenin, which is mainly localized at cellcell junctions, binds to Ecadherin and plays an important role in intercellular adhesion, cell polarity, and architecture (17-19). The downregulation of CXXC finger protein 5 (CXXC5) that increases βcatenin expression (19,20). CXXC5 is significantly downregulated in the corona radiata cells of women with DOR. This downregulation may lead to deterioration of the relationship between cumulus cells and oocytes and, therefore, to oocyte developmental disorders (21). Our patients were women with regulated menstruation who were not diagnosed with DOR or POI before ectopic pregnancy.

Study Limitations

One of the limitations of our study is that AMH levels were lower during pregnancy than in the non-pregnant period. However, while a general value of 1.69 ng/mL has been given in the literature for this value, we found a much lower limit value; therefore, we believe that our study is of some value.

Conclusion

We believe that advanced age is one of the most important factors in the increase in the incidence of ectopic pregnancy, for which there may be many reasons. We found that ovarian reserve was decreased in women who were ectopic. We believe that decreased ovarian reserve in women without risk factors may play a role in the etiology. This finding needs to be confirmed in a larger study.

Ethics

Ethics Committee Approval: According to the Declaration of Helsinki, this prospective study was performed with the permission of the Clinical Research Ethics Committee of a İstanbul Medipol University (dated: 23.06.21, decision no: 731).

Informed Consent: The study was initiated after obtaining detailed verbal and written consent from all participants, with approval from the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K.A., E.E.K., Concept: Ö.K.A., H.G., E.E.K., Design: Ö.K.A., H.G., E.O., D.E.A., Y.A.Ç., Data Collection or Processing: Ö.K.A., E.O., E.E.K., D.E.A., Y.A.Ç., Analysis or Interpretation: Ö.K.A., H.G., E.E.K., Literature Search: Ö.K.A., E.O., E.E.K., D.E.A., Y.A.Ç., Writing: Ö.K.A., H.G.

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ORIGINAL RESEARCH

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Isolated External Auditory Canal Pruritus: A Somatic Obsession

İzole Dış Kulak Yolu Kaşıntısı: Somatik Bir Obsesyon

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Abstract

Objective: Patients presenting to otorhinolaryngology (OHL) clinics with isolated external auditory canal (EAC) pruritus are common. Although there are many etiological reasons for this complaint, psychological factors have long been ignored. Psychocutaneous diseases must be considered in the differential diagnosis when no symptoms that might cause pruritus are detected in the OHL examinations, including anamnesis and microscopic otoscopy, of patients with isolated EAC pruritus. Recent studies have shown that psychological factors or disorders must not be ignored in patients with isolated EAC pruritus.

Method: A total of 60 patients who applied to the OHL clinic with EAC pruritus and had not received psychiatric treatment before or yet were included in the patient group (PG) in the study, after excluding other causes of EAC pruritus. We included 62 individuals in the control group (CG) who had no previous or current complaints of EAC pruritus and who had not received psychiatric treatment. We filled out the sociodemographic data form that we had prepared for the PG and CG participants we included in the study. We also applied the psychiatric symptom screening list (SCL-90-R) and Maudsey obsessive compulsive symptom list (MOCI) scales to the participants. However, we had to exclude 3 of the 62 healthy participants in the control group because they filled out the SCL-90-R and MOCI tests incompletely, and we formed the control group with 59 healthy participants.

Results: The difference between SCL-90-R test overall scores and sub-parameters of SCL-90-R test between PG and CG in our study were the difference between obsessive-compulsive symptoms, somatization, interpersonal sensitivity, depression, anxiety, anger-hostility, phobias, paranoid symptoms, psychoticism and additional scale scores was statistically significant ($p<0.05$). A statistically significant difference was also detected between the MOCI test total scores applied to PG and CG and the MOCI test sub-parameters control, cleanliness, slowness, suspicion, and rumination scores ($p<0.05$).

Conclusion: The data obtained in this study showed that the complaint of isolated EAC pruritus might have a psychological basis. The statistically

Öz

Amaç: Kulak burun boğaz (KBB) polikliniklerine izole dış kulak yolu (DKY) kaşıntısı şikayeti ile başvuran hastalara sık rastlanır. Bu şikayetin bir çok etiyolojik nedeni olmasına rağmen psikolojik faktörler uzun süredir göz ardı edilmektedir. İzole DKY kaşıntısı ile gelen hastaların anamnez ve mikroskopik otoskopilerinide içeren KBB muayenesinde, kaşıntıya sebep olacak bir belirtiye rastlanmadığı zaman ayırıcı tanıda psikokutanöz hastalıklar düşünülmelidir. Son yıllarda yapılan bazı araştırmalar bize, İzole DKY kaşıntısında psikolojik faktörlerin veya psikolojik bozuklukların göz ardı edilmemesi gerektiğini göstermiştir.

Yöntem: Biz çalışmamıza hasta grubu (HG) olarak, DKY kaşıntısı ile KBB polikliniğine başvuran, diğer DKY kaşıntı sebepleri dışlanmış, daha önce ve halen psikiyatrik tedavi almayan 60 hasta aldık. Kontrol grubuna (KG), daha önce veya şimdi DKY kaşıntısı şikayeti olmayan ve psikiyatrik tedavi almayan 62 kişi dahil ettik. Çalışmaya dahil ettiğimiz HG ve KG katılımcılarına kendi hazırladığımız sosyo-demografik veri formunu doldurduk. Katılımcılara ayrıca, ruhsal belirti tarama listesi (SCL-90-R) ve Maudsey obsesif kompülsif semptom listesi (MOKSL) ölçeklerini uyguladık. Fakat kontrol grubuna alınan 62 sağlıklı katılımcıdan 3 kişiyi SCL-90-R ve MOKSL testlerini eksik doldurduğu için çalışma dışı bırakmak zorunda kaldık ve kontrol grubunu 59 sağlıklı katılımcı ile oluşturduk.

Bulgular: Çalışmamızda HG ve KG arasında SCL-90-R testi genel skorları ve SCL-90-R testinin alt parametreleri; obsesif kompülsif belirtiler, somatizasyon, kişiler arası duyarlılık, depresyon, anksiyete, öfke-düşmanlık, fobiler, paranoid belirtiler, psikotizm ve ek skala skorları arasındaki fark istatistiksel olarak anlamlıydı ($p<0,05$). Ayrıca HG ve KG'ye uygulanan MOKSL testi toplam skorları ve MOKSL testi alt parametreleri olan kontrol, temizlik, yavaşlık, kuşku ve ruminasyon puanları arasında istatistiksel olarak anlamlı bir fark olduğu görüldü ($p<0,05$).

Sonuç: Çalışmamızdan elde ettiğimiz veriler bize izole DKY kaşıntısı şikayetinin psikolojik temelli olabileceğini gösterdi. Çalışmamızda iki grup

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Abstract

significant difference in the parameters measuring the obsession and compulsion scores between the two groups in this study suggested that EAC pruritus might be a somatic obsession. Furthermore, the statistically significant difference between all parameters of the scales in the comparison between the two groups supported the hypothesis that EAC pruritus might have a psychological basis. This result, which was detected in the present study, indicated that psychological factors must not be ignored in EAC-related pruritus. However, more extensive studies are needed on this subject.

Keywords: External auditory canal pruritus, obsessive compulsive disorder, psychiatric disorders, somatic obsession

Öz

arasında obsesyon ve kompülsiyon puanlarını ölçen parametrelerdeki istatistiksel olarak anlamlı fark bize DKY kaşıntısının somatik bir obsesyon olabileceğini düşündürdü. Ayrıca iki grup arasındaki karşılaştırmada, uygulanan ölçeklerin tüm parametreleri arasında istatistiksel olarak anlamlı fark olması DKY kaşıntısının psikolojik temelli olabileceği hipotezimizi destekler nitelikteydi. Bizim çalışmamız ile ortaya çıkan bu sonuç, DKY kaşıntısı şikayetinde psikolojik faktörlerin göz ardı edilmemesi gerektiğini gösterdi. Fakat bu konu ile ilgili daha kapsamlı araştırmalara ihtiyaç vardır.

Anahtar kelimeler: Dış kulak yolu kaşıntısı, obsesif kompülsif bozukluk, psikiyatrik bozukluklar, somatik obsesyon

Introduction

The external auditory canal (EAC) or external ear canal is a cartilaginous structure that includes apocrine and sebaceous glands, and the skin contains hairy cells. EAC pruritus or itching is a common symptom of several etiological factors. Various pathologies, such as seborrheic dermatitis, contact dermatitis, dermatomycosis, psoriasis, dermatophyte (Id) reaction, and EAC carcinoma, should be considered as the etiological causes of EAC pruritus (1).

EAC pruritus can be accompanied by pain, burning, or stinging sensations. The severity of itching could be mild or extreme if sleep disturbance is observed in the patient. Patients commonly present in the otorhinolaryngology (OHL) outpatient clinics with only EAC pruritus. This condition was defined as "itchy ear syndrome" in the literature (2). When there is no evidence of bacterial infection, active dermatological disease (psoriasis, atopic dermatitis, etc.), or otomycosis in the OHL examination, which includes anamnesis and microscopic otoscopy, psychocutaneous diseases should be considered in the differential diagnosis. Several psychocutaneous diseases, such as neurodermatitis, primary essential pruritus, and delusional parasitosis, can cause EAC pruritus (3).

Obsessive compulsive disorder (OCD) is characterized by unwanted recurring thoughts (obsessions) and behaviors intended to ward off the anxiety caused by these thoughts (compulsions). There are several types of obsessions and compulsion. Somatic obsessions are only one type of these (4). Somatic obsessions are obsessive and distorted thoughts that can be observed in OCD, and they involve tactility, mobility, or various sensations associated with a certain body part (5). In the literature, certain studies indicated that individuals with obsessive-compulsive personality traits or OCD were more susceptible to EAC pruritus (6). This may be because OCD patients over-focus on the sensations they feel in their bodies. Based on these studies, we concluded that all possible causes of EAC pruritus should be investigated in addition to general anamnesis and examinations in patients who presented to the OHL outpatient clinic with EAC pruritus complaints, and the patient's psychology should be evaluated after all possible organic factors are excluded.

In this study, we set out with the hypothesis that pruritus in patients with EAC pruritus may have a psychological cause when other causes of EAC pruritus are excluded and that this condition may be a somatic obsession (3,5). For this purpose, routine oto-microscopic external ear canal evaluation was performed in patients included in the study. The examinations were performed by the same otolaryngologist using the same ear microscope in a similar manner for all patients. We applied the symptom checklist (SCL-90-R) and the Maudsley Obsessive-Compulsive Inventory (MOCI) to the patient group (PG) and healthy control group (CG) and compared the results between the two groups.

Materials and Methods

Sixty (n=60) 18-65-year-old patients who presented to the OHL outpatient clinic at Mardin Training and Research Hospital with pruritus compliance and voluntarily agreed to participate were included in the study. In addition to a detailed ear, nose, and throat examination, microscopic examination of the EAC and external ear auditory secretion was conducted to exclude infectious and allergic factors that could cause EAC pruritus.

We included 62 individuals in the control group (CG) who had no previous or current complaints of EAC pruritus and who had not received psychiatric treatment. We filled out the socio-demographic data form that we had prepared for the PG and CG participants we included in the study. We also applied the psychiatric symptom screening list (SCL-90-R) and Maudsey obsessive compulsive symptom

list (MOCI) scales to the participants. However, we had to exclude 3 of the 62 healthy participants in the control group because they filled out the SCL-90-R and MOCI tests incompletely, and we formed the control group with 59 healthy participants.

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Mardin Artuklu University (date: 06/04/2022, number: 2022-7). Approval of the participants included in the study was obtained using a voluntary consent form.

Data Collection Instruments

Socio-demographic participant data were collected using a form developed by the authors. SCL-90-R and MOCI were also applied to the participants.

SCL-90-R

SCL-90-R is a 90-item checklist developed by Derogatis (7). This test is used to screen for psychological symptoms, including somatization, obsessive-compulsive symptoms, interpersonal sensitivity, anxiety, depression, phobia, anger/hostility, paranoid traits, psychoticism, an additional scale and general evaluation items. The validity and reliability of the Turkish version of the scale were determined by Dağ (8).

MOCI

The MOCI was developed by Hodgson and Rachman (9) to investigate the type of OCD symptoms and was validated in the Turkish language by Erol and Savaşır (10). The inventory includes checking, cleaning, slowness, doubting, and rumination subdimensions.

Statistical Analysis

IBM SPSS 21.0 for Windows statistical software was used for the statistical analysis of the study data. Measured variables are presented as mean ± standard deviation and median, and categorical variables are presented as counts and percentages (%). The normal distribution of the data was checked. The Mann-Whitney U test was employed to compare group data without normal distribution. The chi-square (χ^2) test was employed to compare qualitative variables between the groups. P<0.05 was accepted as statistically significant.

Results

The hg included 46 females (n=46, 76.7%), 14 males (n=14, 23.3%), 60 (n=60) participants. The CG included 41 women (n=41, 69.5%) and 18 men (n=18, 30.5%); a total of 59 (n=59) participants. The socio-demographic data are presented in Table 1.

The age and employment status of the patient and CGs were statistically similar. The distribution of participants according to gender and education level was different (p<0.05, Table 1).We determined that the difference between the general evaluation scores of the patient and CGs was statistically significant in the SCL-90-R. Furthermore, the differences between obsessive-compulsive symptoms, somatization, interpersonal sensitivity, depression, anxiety, anger-hostility, phobia, paranoid symptoms, psychoticism subdimension, and additional scale scores of the groups were statistically significant in the SCL-90-R (p<0.001, Table 2).

The difference between the total scores of the two groups in the MOCI was statistically significant. The difference between the MOCI checking, cleaning, slowness, doubting, and rumination subdimension scores of the PG and CG was statistically significant (p<0.001, Table 3).

Discussion

Isolated EAC pruritus is a common symptom, the etiology of which is still not clear. The literature generally reported

Table 1. Comparison of socio-demographic data of PG and CG

		PG (n=60)	CG (n=59)	p (p<0.05)
Age (mean ± SD)		31.10±10.55	32.95±5.59	0.234
Gender	Female	46 (76.7%)	41 (69.5%)	<0.001
	Male	14 (23.3%)	18 (30.5%)	
Employment	Employed	60 (100%)	53 (89.9%)	0.034
	Unemployed	0 (0%)	6 (10.2%)	
Education	Primary school	2 (3.3%)	4 (6.8%)	0.005
	Middle school	14 (23.3%)	10 (16.9%)	
	High school	24 (40.0%)	26 (44.1%)	
	College	20 (33.3%)	19 (32.2%)	

PG: Patient group, CG: Control group, n: Count, SD: Standard deviation, p: Mann-Whitney U test statistical significance: (p<0.05)

that allergic contact dermatitis is responsible for the etiology of isolated ear itching (11). However, Acar et al. (12) reported that patients with isolated EAC pruritus did not exhibit allergic contact dermatitis symptoms on histopathological analysis (12). Therefore, there is no consensus on the underlying pathology of isolated EAC pruritus, and the etiologic factors have not been completely determined (13). Due to this uncertainty, patients are frequently diagnosed with idiopathic EAC pruritus. However, recent studies have demonstrated

Table 2. Comparison of the study groups based on symptom checklist (SCL-90-R) and subdimension scores

SCL-90-R	Group	n	Median	Mean ± SD	Mean Rank	U	p
General evaluation	PG	60	1.23	1.20±0.74	78.23	676.000	<0.001
	CG	59	0.31	0.36±0.33	41.46		
Somatization	PG	60	1.29	1.45±0.99	81.45	483.000	<0.001
	CG	59	0.25	0.34±0.27	38.19		
Obsessive compulsive symptoms	PG	60	1.60	1.54±0.84	80.58	535.000	<0.001
	CG	59	0.30	0.43±0.38	39.07		
Interpersonal sensitivity	PG	60	1.39	1.20±0.92	71.45	1083.000	<0.001
	CG	59	0.23	0.42±0.40	48.36		
Depression	PG	60	1.27	1.22±0.87	75.55	837.000	<0.001
	CG	59	0.23	0.37±0.39	44.19		
Anxiety	PG	60	1.05	1.15±0.88	77.82	701.000	<0.001
	CG	59	0.20	0.32±0.33	41.88		
Anger-hostility	PG	60	1.17	1.00±0.78	74.05	927.000	<0.001
	CG	59	0.17	0.38±0.55	45.71		
Phobia	PG	60	0.70	0.86±0.73	77.12	743.000	<0.001
	CG	59	0.14	0.23±0.32	42.59		
Paranoid traits	PG	60	1.00	1.10±0.88	71.75	1065.000	<0.001
	CG	59	0.33	0.50±0.58	48.05		
Psychoticism	PG	60	0.75	0.80±0.78	71.70	1068.000	<0.001
	CG	59	0.10	0.27±0.33	48.10		
Additional scale	PG	60	1.14	1.20±0.90	74.77	884.000	<0.001
	CG	59	0.29	0.44±0.50	44.98		

PG: Patient group, CG: Control group, SCL-90-R: Symptom checklist, n: Count, SD: Standard deviation, U: Mann-Whitney U test, p: Mann-Whitney U test statistical significance: (p<0.05)

Table 3. Comparison of the MOCI total and subdimension scores of study groups

MOCI	Group	n	Median	Mean ± SD	Mean Rank	U	p
Total	PG	60	20.00	20.53±7.85	84.87	278.000	<0.001
	CG	59	7.00	7.31±4.76	34.71		
Checking	PG	60	5.00	4.33±2.65	80.47	542.000	<0.001
	CG	59	1.00	1.15±1.40	39.19		
Cleaning	PG	60	7.00	7.10±2.53	82.68	409.000	<0.001
	CG	59	3.00	3.10±2.05	36.93		
Slowness	PG	60	2.00	2.83±1.91	76.48	781.000	<0.001
	CG	59	0.00	0.98±1.18	43.24		
Doubting	PG	60	4.50	4.27±1.56	84.53	298.000	<0.001
	CG	59	2.00	1.59±0.95	35.05		
Rumination	PG	60	2.00	1.93±1.45	77.02	749.000	<0.001
	CG	59	0.00	0.48±0.77	42.69		

PG: Patient group, CG: Control group, MOCI: Maudsley Obsessive-Compulsive Inventory, n: Count, SD: Standard deviation, U: Mann-Whitney U test, p: Mann-Whitney U test statistical significance: (p<0.05)

that psychological factors (e.g., somatization disorder) should be kept in mind as well as other etiologies in patients with EAC pruritus complaints before describing the symptoms as idiopathic (14).

It has been known for a long time that psychological factors can be effective in the treatment of itching in general (15). The degree of depression or anxiety symptoms was directly associated with the severity of itching in various pruritic skin diseases (16-18). It is also known that itching severity can increase in patients with psychiatric disorders (19,20). Pruritus strongly reduces quality of life and can often be comorbid with other psychiatric disorders, including suicidal ideation (21). Studies have reported a positive correlation between pruritus and depression scores. Patients with high depression scores scored higher on the itching severity test than those with low depression scores (22).

Psychogenic pruritus can accompany other psychiatric conditions, such as depression, anxiety, obsessive-compulsive disorder, psychosis, and substance use (18,23,24). Pruritus is also a symptom of somatoform dissociation, and even milder degrees of dissociation may play a role in the development of psychogenic pruritus (25). Thus, the psychological state of patients with persistent itching should be considered. This approach may also be applicable to isolated EAC pruritus (26).

The obsessions and compulsion observed in OCD patients tend to change over time. Somatic obsessions are among the types of obsessions. Somatic obsessions are when individuals with OCD become excessively interested in any part of their body and/or focus their thoughts on it, causing them to perceive minimal or non-existent physical symptoms more intensely and develop obsessions and compulsions about this issue over time (27). In OCD, somatic obsession can be recognized as abnormal body awareness (27). The following bodily processes are common in individuals who suffer from somatic obsessions: breathing, blinking, salivation, and swallowing; body position; tactile sensations such as heartbeat or itching, tinnitus, “floaters in eyesight”, and other visual distractions (e.g., seeing the profile of own nose in peripheral vision) (6).

Yilmaz et al in a 2016 study, Yilmaz et al. (26) claimed that almost half (43%) of patients with isolated ear canal pruritus had a type D personality. These individuals have high levels of anxiety, worry about unimportant thoughts or behaviors, over-attribute thoughts, are introverted, have high social shyness, and fear rejection or disapproval (28). Type D personality has recently been associated with various diseases, such as irritable bowel syndrome, heart disease, anal fissures, type 2 diabetes, and hemorrhoids (29,30). Yilmaz et al. (26) reported that patients with type D personality experienced more severe pruritus than controls, and higher depressive and anxiety symptoms were observed in these patients than in controls. Furthermore, there was a negative correlation between the extraversion dimension score of the revised Eysenck personality questionnaire short form score and the severity of pruritus (26). Before these patients are diagnosed with idiopathic EAC pruritus, they should undergo a psychiatric examination (26).

The present study findings confirmed that EAC pruritus can be induced by psychological factors. We observed a significant difference between the general evaluation and other subdimension SCL-90-R scores of the patients and CG. Among these parameters, the high obsessive comppulsion, anxiety, depression, somatization, interpersonal sensitivity, phobia, anger-hostility and other scores in the PG supported our hypothesis. In the CG, the general evaluation and subdimension scores were lower than those in the HG. These findings suggested that the HG exhibited more psychiatric symptoms.

A review of type D personality traits would reveal similarities with OCD-associated traits, especially perfectionism, social inhibition, and introversion. Thus, the MOCI was applied to PG and CG in our study, and we observed that the findings were more significant than expected. The checking, cleaning, slowness, doubting, and rumination subdimension scores of the HG were significantly higher than those of the CG. There were statistically significant differences between the subdimension scores of the two groups.

Study Limitations

However, the scarcity of similar studies in the literature, the small sample size of the current study, and the fact that some biochemical diagnostic tests were not applied prevented generalization of the hypothesis. These are the limitations of our study. Therefore, more comprehensive analytical studies should be conducted on the same patient population and on patients with OCD and somatic obsessions.

Conclusion

The findings of this study strongly supported the hypothesis and suggested the following: Is EAC pruritus an obsession, and in particular, is it a type of somatic obsession? Both the SCL-90-R and MOCI scores demonstrated that individuals with EAC pruritus should undergo a psychiatric examination after excluding other etiologic factors.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Mardin Artuklu University (date: 06/04/2022, number: 2022-7).

Informed Consent: Approval of the participants included in the study was obtained using a voluntary consent form.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., S.K.D., B.S., Concept: M.A., S.K.D., B.S., Design: M.A., S.K.D., B.S., Data Collection or Processing: M.A., S.K.D., B.S., Analysis or Interpretation: M.A., S.K.D., B.S., Literature Search: M.A., S.K.D., B.S., Writing: M.A., S.K.D., B.S.

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ORIGINAL RESEARCH

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Evaluation of HIV Patients in the Intensive Care Unit: A Single-center Experience

Yoğun Bakım Ünitesinde HIV Hastalarının Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Objective: Human immunodeficiency virus (HIV)-positive patients are admitted to intensive care units (ICU) due to various diseases, whether or not related to HIV. The characteristics of HIV-positive patients who were followed up in ICUs have also changed over the years. In this study, we aimed to evaluate the demographic data, laboratory findings, indication for admission, and mortality rate of HIV-positive patients admitted to ICU.

Method: The data of HIV-positive patients admitted to the ICU of University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2012 and January 2024 were retrospectively examined in this study. Patients >18 years of age who were detected to be anti-HIV positive by enzyme-linked immunosorbent assay before admission to ICU or during follow-up in ICU and who had Western Blot confirmation were included. Demographic characteristics of the patients, the reason for admission, comorbidities, acute physiology and chronic health evaluation II score, and laboratory findings were recorded through the hospital information system.

Results: Sixty-two patients with HIV admitted to the ICU were included in the study. Forty-five (72.5%) patients were male and 17 (27.4%) were female. 85.4% of patients required mechanical ventilation. Mortality was 69.3%. In non-survivors, the platelet and lymphocyte counts were statistically significantly lower than survivors (p=0.01). The duration of mechanical ventilation was shorter in survivors (p=0.01). CD4 T lymphocyte counts were statistically significantly lower in non-survivors (p=0.01). There was no relationship between HIV RNA level and mortality (p=0.06). The presence of viral hepatitis was associated with mortality (p=0.01).

Öz

Amaç: Yoğun bakım üniteleri (YBÜ), insan immün yetmezlik virüsü (HIV) pozitif hastaları, HIV ile ilişkili olsun ya da olmasın çeşitli hastalıklar nedeniyle kabul etmektedir. Zamanla YBÜ'lerinde izlenen HIV pozitif hastaların özelliklerinde de değişiklikler olmuştur. Bu çalışmayı yapmaktaki amacımız YBÜ'ye kabul edilen HIV pozitif hastaların özelliklerini, laboratuvar bulgularını, kabul koşullarını ve mortalite oranlarını değerlendirmektir.

Yöntem: Bu çalışmada Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma YBÜ'ye Ocak 2012 ile Ocak 2024 tarihleri arasında başvuran HIV pozitif hastaların verileri retrospektif olarak incelenmiştir. YBÜ'ye alınmadan önce veya yoğun bakımda takip sırasında enzim bağlantılı immünosorbent testi ile anti-HIV pozitif olduğu tespit edilen ve Western Blot onayı olan, 18 yaş üstü hastalar çalışmaya dahil edildi. Hastaların demografik özellikleri, başvuru tanıları, yandaş hastalıkları, akut fizyoloji ve kronik sağlık değerlendirmesi II skoru ve laboratuvar bulguları hastane bilgi sistemi üzerinden kaydedildi.

Bulgular: YBÜ'ye kabul edilen 62 HIV hastası çalışmaya dahil edildi. Hastaların 45'i (%72,5) erkek, 17'si (%27,4) kadındı. Hastaların %85,4'ünün mekanik ventilasyon gereksinimi oldu. Mortalite oranı %69,3 olarak bulundu. Hayatta kalmayanlarda trombosit ve lenfosit sayıları hayatta kalanlara göre istatistiksel olarak anlamlı derecede düşüktü (p=0,01). Hayatta kalanlarda mekanik ventilasyon süresi daha kısaydı (p=0,01). CD4 T lenfosit sayıları hayatta kalmayanlarda istatistiksel olarak anlamlı derecede düşüktü (p=0,01). HIV RNA düzeyi ile mortalite arasında ilişki saptanmadı (p=0,06). Viral hepatitin varlığı mortalite ile ilişkili bulundu (p=0,01).

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Abstract

Conclusion: More patients with HIV are admitted to ICUs. In our study, the platelet, lymphocyte, and CD4 T lymphocyte counts were lower in non-survivors than in survivors at ICU admission. Duration of mechanical ventilation and presence of viral hepatitis were associated with mortality. These parameters can be used as mortality indicators upon admission to the ICU.

Keywords: HIV, intensive care unit, mortality

Öz

Sonuç: YBÜ'ye daha fazla HIV hastası kabul edilmektedir. Çalışmamızda, hayatta kalmayanların YBÜ'ye kabul sırasında trombosit, lenfosit ve CD4 T lenfosit sayıları hayatta kalanlara göre daha düşüktü. Mekanik ventilasyonun süresi ve viral hepatitin varlığı mortaliteyle bağlantılıydı. Bu faktörler YBÜ'ye kabul sırasındaki mortaliteyi tahmin etmek için kullanılabilir.

Anahtar kelimeler: HIV, mortalite, yoğun bakım ünitesi

Introduction

Human immunodeficiency virus (HIV)/AIDS; has been affecting more and more people every day since it was identified in 1981. It is an important public health problem that causes medical, social, and economic issues. According to the World Health Organization (WHO), the number of people with HIV infection worldwide is estimated to reach 39.0 million, and 1.3 million new cases will be identified by the end of 2022. The global incidence of HIV has decreased since 2015. However, it increases by 45% in the Eastern Mediterranean region, which includes Turkey (1). The ministry of health of Turkey reported that 39,437 people were HIV-positive in Turkey between 1985 and 2023. An increase in the incidence of the disease has been observed over the years. HIV prevalence is reported to be 0.1 per 100,000 in Turkey (2).

Unlike the years in which HIV was first identified, the aggressive course of the disease can now be controlled in many cases with the widespread use of combined antiretroviral treatments. Effective prevention, diagnosis, treatment, and care of HIV have made HIV a manageable disease. Therefore, people can live with it for a long time. As a result, patients die more frequently from comorbidities (3,4). Unawareness of HIV positivity may cause disease progression without any treatment and present itself with opportunistic infections as a result of severe immunosuppression (5).

HIV-positive patients have been admitted to intensive care units (ICU) due to various diseases, whether or not (3,4). The characteristics of HIV-positive patients who were followed up in ICUs have also changed over the years. Although it can be expected that the ICU admission rates of HIV-infected individuals will generally decrease after antiretroviral treatment, hospitalizations due to HIV treatment toxicity and non-HIV-related diseases occur worldwide (5,6).

Because of the increase in the incidence of HIV in Turkey, it has become more important to prevent delays in diagnosis, treatment, and death and to decrease the costs of this manageable disease. In this study, we aimed to evaluate the demographic data, laboratory findings, reason for admission, and mortality rate of HIV-positive patients admitted to the ICU.

Materials and Methods

The data of HIV-positive patients admitted to the ICU of University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2012 and January 2024 were retrospectively examined in this study. Patients >18 years of age who were detected to be anti-HIV positive by enzyme-linked immunosorbent assay at the time of admission to ICU or during follow-up in ICU and who had Western Blot confirmation were included. Patients with coronavirus disease-19 were not included in the study. Demographic characteristics of the patients, diagnosis of admission, comorbidities such as diabetes mellitus, hypertension acute physiology and chronic health evaluation (APACHE) II score, laboratory findings at admission to ICU, characteristics special for ICU such as length of stay, and duration of mechanical ventilation were recorded through the hospital information system. Patients had various comorbidities, and we classified them according to whether at least one comorbidity exists or not.

Ethics committee approval for this retrospective study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (date: 19.08.2022, decision no: 261). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using SPSS 22 software. The distribution of variables was tested by Kolmogorov-Simirnov test. When the normality assumption was not met, non-parametric tests were used. Mann-Whitney U test were used to compare two independent groups. The chi-square test and the Fisher's exact test were used to examine the relationship between categorical variables.

A significance level of 0.05 was considered statistically significant.

Results

Sixty-two patients with HIV admitted to the ICU in University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2012 and January 2024 were included in the study. Forty-five (72.5%) of the patients were male and 17 (27.4%) were female. The average age was 48.14±14.1 years, the youngest patient was 24 years old, and the oldest patient was 89 years old. Although 41 (66.1%) patients were diagnosed with HIV at admission to the ICU, the anti-HIV positivity of 21 (33.8%) patients was known before admission to the ICU. In total, 40 (64.5%) patients received any antiretroviral agent during the follow-up in the ICU. Thirty-seven (59.6%) patients were admitted to the ICU from other services, 25 (40.3%) patients were admitted from emergency service to ICU. Thirty-two (51.6) patients were admitted to the ICU for respiratory reasons, 22 (35.4%) patients were admitted to the ICU for neurological reasons, 5(8.0%) patients were admitted to the ICU for postoperative care, and 3 (4.8%) patients were admitted to the ICU for cardiac reasons. Thirty-five (56.4%) patients had no comorbidities. However, there were 8 patients with hypertension, 5 patients with diabetes mellitus, 4 patients with chronic renal disease, 4 patients with chronic obstructive pulmonary disease, 2 patients with asthma, 3 patients with congestive heart failure, 1 patient with coronary artery disease.

At the time of intensive care admission, 20 (32.2%) patients had acute hepatic failure, and 35 (37.1%) had acute kidney failure. There was at least one positive viral hepatitis test in 12 (19.3%) patients. Viral hepatitis markers were negative in 50 (80.6%) patients. During the ICU follow-up, 53 (85.4%) patients required mechanical ventilation. Tracheostomy was performed in 9 of these patients in the ICU. In 27 (43.5%) patients, at least one culture sample was positive. Twelve (19.3%) patients were diagnosed with tuberculosis. Five (8%) patients received antituberculosis therapy for tuberculosis. In 45 (72.5%) patients, there was no evidence of tuberculosis. Mortality was 69.3%. Nineteen (30.6%) patients were discharged from the ICU to services. The number of patients with HIV follow-up in the ICU was 17 in 2023 and 2 in 2012. The number of patients increased over time (Figure 1).

There was no significant difference between non-survivors and survivors in terms of APACHE II score, length of hospital stay, and length of stay in ICU (respectively p=0.35, p=0.31 and p=0.99). The duration of mechanical ventilation was shorter in survivors (p=0.01). The relationship between ICU characteristics and mortality is presented in Table 1. There was no significant difference between non-survivors and survivors in terms of the reason for admission to the ICU (p=0.33). The presence of tuberculosis was not associated with mortality

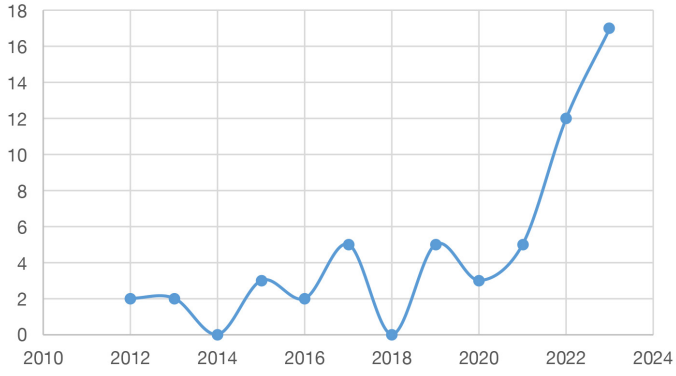

Figure 1. Number of patients with HIV admitted to the intensive care unit over the past years
HIV: Human immunodeficiency virus

Table 1. The relationship between the characteristics special for ICU and mortality

Variable	Group	n		Median (Ranj)	z	p
Length of stay in ICU (day)	Non-survivors	43	15.63±18.13	8.00 (72.00)	-0.02	0.99
	Survivors	19	15.53±20.99	6.00 (83.00)		
APACHE II	Non-survivors	43	20.40±11.39	18.00 (61.00)	-1.02	0.31
	Survivors	19	16.89±8.99	18.00 (38.00)		
Length of hospitalization (day)	Non-survivors	43	25.05±23.81	18.00 (109.00)	-1.02	0.31
	Survivors	19	33.11±29.85	20.00 (98.00)		
Duration of mechanical ventilation (day)	Non-survivors	43	14.14±18.50	7.00 (84.00)	-2.48	**0.01**
	Survivors	19	10.21±20.74	2.00 (84.00)		

z: Mann-Whitney U test, APACHE: Acute physiology and chronic health evaluation, ICU: Intensive care unit, SD: Standard deviation

(p=0.86). The presence of viral hepatitis was associated with mortality (p=0.01). Existence of any comorbidities, such as diabetes mellitus, hypertension, or chronic heart failure, was not associated with mortality. There was no relationship between HIV RNA level and mortality (p=0.06). The relationship between patient characteristics upon admission to the ICU and mortality is presented in Table 2. Hemoglobin, hematocrit, white blood cell, procalcitonin, and lactate levels measured at the time of intensive care admission were similar in both non-survivors and survivors (p>0.05). However, in non-survivors, the platelet and lymphocyte counts were statistically significantly lower than survivors (p=0.01). CD4 T lymphocyte counts were statistically significantly lower in non-survivors (p=0.01). The relationship between laboratory findings upon admission to the ICU and mortality is presented in Table 3.

Table 2. The relationship between the characteristics at admission into ICU and mortality

Variable	Group	Mortality				X^2	p
		Non-survivors		Survivors			
		n	%	n	%		
The reason for admission	Cardiac	3	100.00	0	0.00	3.46*	0.33
	Neurological	15	68.18	7	31.82		
	Postoperative	2	40.00	3	60.00		
	Respiratory	23	71.88	9	28.13		
The presence of at least one comorbidity	Yes	19	70.37	8	29.63	0.02	0.88
	No	24	68.57	11	31.43		
Viral hepatitis	Yes	12	100.00	0	0.00	6.58*	**0.01**
	No	31	62.00	19	38.00		
HIV RNA (copy/mL)	<10000	2	33.33	4	66.67	5.66*	0.06
	>10000	27	75.00	9	25.00		
	Not detected	2	40.00	3	60.00		
Presence of tuberculosis	Yes	8	66.67	4	33.33	0.31	0.86
	Suspicious	4	80.00	1	20.00		
	No	31	68.89	14	31.11		

X^2: Chi-square test, *: Fisher's exact test, HIV: Human immunodeficiency virus, ICU: Intensive care unit

Table 3. The relationship between the laboratory findings at admission into ICU and mortality

Variable	Group	n		Median (Ranj)	z	p
CD4 (cells/mm³)	Non-survivors	40	94.97±187.15	43.50 (1122.00)	-2.63	**0.01**
	Survivors	17	165.72±147.88	139.90 (494.00)		
	Survivors	19	15.53±20.99	6.00 (83.00)		
Lactate (mmol/L)	Non-survivors	40	2.51±2.82	1.88 (14.40)	-1.05	0.29
	Survivors	18	1.74±0.92	1.61 (4.02)		
Procalcitonin (µg/L)	Non-survivors	43	8.65±22.43	0.32 (100.00)	-0.68	0.49
	Survivors	19	4.70±16.48	0.34 (72.49)		
Hemoglobin (g/dL)	Non-survivors	43	9.90±2.17	9.70 (8.70)	-1.15	0.25
	Survivors	19	10.58±2.79	10.30 (11.30)		
Hematocrite (%)	Non-survivors	43	29.63±6.57	28.10 (26.90)	-1.03	0.30
	Survivors	19	31.43±7.78	29.40 (32.60)		
White blood cell count (10^9/L)	Non-survivors	43	7.25±6.18	6.73 (21.49)	-1.83	0.07
	Survivors	19	11.19±7.76	9.09 (31.00)		
Platelet (10^9/L)	Non-survivors	43	148.70±111.48	117.00 (382.00)	-2.75	**0.01**
	Survivors	19	248.84±145.75	215.00 (689.00)		
Lymphocyte (10^9/L)	Non-survivors	43	0.56±0.55	0.44 (2.50)	-2.77	**0.01**
	Survivors	19	5.16±18.14	0.86 (79.90)		

z: Mann-Whitney U test, ICU: Intensive care unit

Discussion

In the study, the number of patients with HIV who were followed up in our unit increased over the years. According to the WHO, the incidence of HIV has increased in the Eastern Mediterranean region (1). Our study may reflect this course. The gender statistics in this study are similar to those in the literature. It was reported that 81.5% of HIV-positive individuals were male, and 18.5% were female in Turkey (2). It is impressive that mortality is high. Only 19 (30.6%) patients were discharged from the ICU to services. It is higher than that of recent studies (6). The course of HIV infection has changed considerably since the 1990s with the introduction of antiretroviral drugs. This approach also affected the profile of HIV-positive patients admitted to the ICU. When the epidemic first emerged, most patients were hospitalized due to complications of HIV infection, such as sepsis. In recent years, life expectancy has been extended with effective treatments, and the number of patients admitted to the ICU for non-HIV-related reasons has increased (7). Only 21 patients had a diagnosis of HIV before admission to the ICU, and 40 patients could receive antiretroviral drugs. The low percentage of patients who were aware of HIV positivity before admission to the ICU was remarkable. In our study, the most common reason for admission to the ICU was respiratory distress (51.61%). This finding is consistent with the literature from the early 2000s (8). Patients may be admitted during advanced disease, which can be the main cause of high mortality. The high mortality rate may also be related to the presence of viral hepatitis. There was found that the presence of viral hepatitis and mortality in this study. All patients with viral hepatitis died. It has been reported that viral hepatitis can also increase mortality (9,10). Not receiving any antiretroviral drug may worsen the outcome, also (11). Studies have shown that comorbidities become more frequently the reason for mortality in HIV-positive patients after antiretroviral drug use, and the need for mechanical ventilation and hospitalization for HIV-related disease are associated with mortality (12). In this study, comorbidities were not associated with mortality. APACHE II score, length of hospital stay, and length of ICU stay were similar between survivors and non-survivors with HIV in ICU. Mechanical ventilation support was required in 85.48% of patients. The duration of mechanical ventilation was statistically significantly shorter in patients discharged. The need for mechanical ventilation was associated with mortality, consistent with the literature (6). This result shows that the profile of patients in the study was similar to that of patients in the early period of the epidemic. Similar to recent studies, in non-survivors, the platelet, lymphocyte, and CD4 T lymphocyte counts were lower than those in survivors at admission to the ICU (6). These parameters can be used as mortality indicators upon admission to the ICU.

Conclusion

The incidence of HIV positivity also increases. More patients with HIV are admitted to ICUs. In our study, the platelet, lymphocyte, and CD4 T lymphocyte counts were lower in non-survivors than in survivors at ICU admission. Duration of mechanical ventilation and presence of viral hepatitis were associated with mortality. These parameters can be used as mortality indicators upon admission to the ICU. Further studies are required.

Ethics

Ethics Committee Approval: Ethics committee approval for this retrospective study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (date: 19.08.2022, decision no: 261). This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained verbally and in writing from all participants.

Footnotes

Authorship Contributions

Concept: S.B., A.N.S., D.N.S., Design: S.B., A.N.S., D.N.S., Data Collection or Processing: S.B., A.N.S., D.N.S., Analysis or Interpretation: S.B., A.N.S., Literature Search: S.B., A.N.S., D.N.S., Writing: S.B., A.N.S., D.N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Anatomical Risk Factors Identifiable on Computed Tomography in Otosclerosis

Otosklerozda Bilgisayarlı Tomografide Demonstre Edilebilen Anatomik Risk Faktörleri

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Abstract

Objective: The aim of the current study was to evaluate the relationship between the dimensions of the temporal bone, high-riding jugular bulbs, and jugular bulb dehiscence in patients with otosclerosis compared with healthy controls.

Method: Two radiologists retrospectively evaluated high-resolution computed tomography images of the temporal bone from 34 patients radiologically diagnosed with otosclerosis, along with images from 34 age- and sex-matched control subjects for comparison. Measurements of temporal bone, including the length and width of the petrous bone and the angle between the midsagittal line and the petrous bone, were performed on a defined standardized slice orientation using a workstation. High-riding jugular bulbs and jugular bulb dehiscence were noted in both groups.

Results: The study cohort of 68 subjects (34 patients and 34 controls) with an average age of 48.08±11.23 years showed no significant differences in the presence of high jugular bulbs and jugular bulb dehiscence. The lengths, widths, and angles of the petrous bone were similar in both groups when analyzed bilaterally, as well as in comparisons between the affected sides of patients and the corresponding sides of the healthy controls.

Conclusion: The current study revealed that neither high-riding jugular bulb nor jugular bulb dehiscence was significantly associated with otosclerosis. Additionally, the dimensions of the petrous part of the temporal bone were not associated with the disease. Identifying the anatomical factors associated with or not associated with otosclerosis can be instrumental in clarifying its etiology and guiding future research toward a more comprehensive understanding of the disease.

Keywords: Fissula ante fenestram, jugular bulb, otosclerosis, temporal bone

Öz

Amaç: Bu çalışmanın amacı, otoskleroz hastalarında temporal kemiğin boyutları, yüksek konumlu juguler bulbus ve juguler bulbus dehisansı ile olan ilişkileri sağlıklı kontrollerle karşılaştırmalı olarak değerlendirmektir.

Yöntem: Otoskleroz tanılı 34 hasta ve yaş ve cinsiyet açısından eşleştirilmiş 34 kontrolün temporal kemiğine ait yüksek çözünürlüklü bilgisayarlı tomografi görüntülerini iki radyolog retrospektif olarak değerlendirmiştir. Temporal kemik ölçümleri, belirlenen standart kesitte bir iş istasyonu kullanılarak gerçekleştirilmiş ve petroz kemiğin uzunluğu, genişliği ve midsagittal çizgi ile petroz kemiği arasındaki açı ölçülmüştür. Her iki grupta da yüksek konumlu juguler bulbus ve juguler bulbus dehisansı not edilmiştir.

Bulgular: Ortalama yaşı 48,08±11,23 yıl olan 68 katılımcı (34 hasta ve 34 kontrol) arasında yüksek juguler bulbus ve juguler bulbus dehisansının varlığı açısından anlamlı bir fark bulunmamıştır. Petroz kemiğin uzunlukları, genişlikleri ve açıları, her iki grup arasında ve aynı zamanda hastaların etkilenen tarafları ile sağlıklı kontrollerin karşılık gelen tarafları arasında yapılan karşılaştırmalarda benzer bulunmuştur.

Sonuç: Bu çalışma, yüksek konumlu juguler bulbusun ve juguler bulbus dehisansının otoskleroz ile anlamlı bir ilişkisi olmadığını ortaya koymaktadır. Ayrıca, temporal kemiğin petroz kısmının boyutları da hastalıkla herhangi bir ilişki göstermemiştir. Otoskleroz ile ilişkili ya da ilişkisiz olan anatomik faktörlerin belirlenmesi, hastalığın etiyolojisinin açıklanmasına yardımcı olabilir ve hastalığın daha kapsamlı anlaşılması yönünde gelecekteki araştırmalara rehberlik edebilir.

Anahtar kelimeler: Fissula ante fenestram, juguler bulbus, otoskleroz, temporal kemik

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Introduction

Otosclerosis, also known as otospongiosis, is a primary osteodystrophy of the otic capsule and is a major cause of acquired hearing loss in adults. Otosclerosis is generally considered idiopathic and involves complex remodeling and subsequent fixation of the stapes bone. Such fixation significantly impairs the transmission of sound to the inner ear, potentially leading to conductive, sensorineural, or mixed types of hearing loss and results in progressive auditory impairment (1). Otosclerosis manifests in two primary forms: fenestral and retrofenestral. The fenestral type, also known as the stapedial type, primarily affects the oval window and stapes footplate. In this form, hearing loss is predominantly conductive, resulting from the thickening and fixation of stapes. On the other hand, the retrofenestral or cochlear type involves the cochlea and involves demineralization of the cochlear capsule. This typically results in sensorineural hearing loss, although the exact mechanism remains unclear. In retrofenestral otosclerosis, the prefix "retro" indicates "behind" or "deep to," rather than "posterior," referencing the medial wall of the middle ear as observed through otoscopy. Often presenting alongside fenestral involvement, these two manifestations are not separate entities; rather, they point toward a continuum, highlighting the progressive and interconnected nature of the condition (2). Retrofenestral otosclerosis is characterized by areas of demineralized spongy vascular bone within the cochlear capsule, which may further encroach upon the vestibule, semicircular canals, and internal auditory canal (Figure 1). The promontory often exhibits a pinkish hue visible through the tympanic membrane, a phenomenon known as the Schwartze sign (1,3,4). The etiology of sensorineural hearing loss in this context is hypothesized to stem from direct damage to the cochlea and spiral ligament due to lytic activity or the release of proteolytic enzymes (1,3,4). In fenestral otosclerosis, the disease process primarily targets the lateral wall of the bony labyrinth, with spongy new bone typically developing in the area of the fistula ante fenestrae. The latter is a fibrocartilaginous cleft located just anterior to the oval window, bridging the inner and middle ear (Figure 2). The pathology gradually progresses to encompass the entire footplate of the stapes, potentially extending to the cochlea. Involvement of the annular ligament induces mechanical fixation at the stapedo-vestibular joint, culminating in characteristic conductive hearing loss and an audiometric air-bone gap, often referred to as Carhart's notch (1,4).

Although the precise etiology of otosclerosis remains elusive, genetic predisposition is widely believed to contribute significantly to its development (5,6). This phenomenon is also associated with potential factors such as viral infections, disrupted bone metabolism, inflammatory and hormonal dynamics, and autoimmune responses (7,8). In addition to these factors, the relationship between anatomical characteristics and otosclerosis was evaluated. Temporal changes in bone size or shape can influence sound transmission mechanics in the middle and inner ear. Deviations in dimensions like the petrous bone length or cochlear aqueduct width may alter ossicle

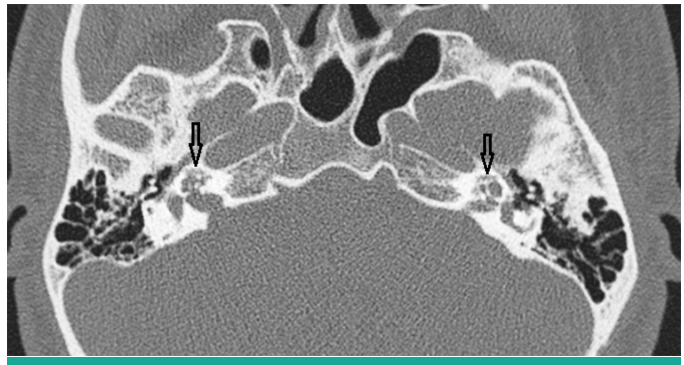

Figure 1. Temporal high-resolution computed tomography scan of a 27-year-old male patient presenting with tinnitus revealed bilateral retrofenestral otosclerosis, as indicated by black arrows

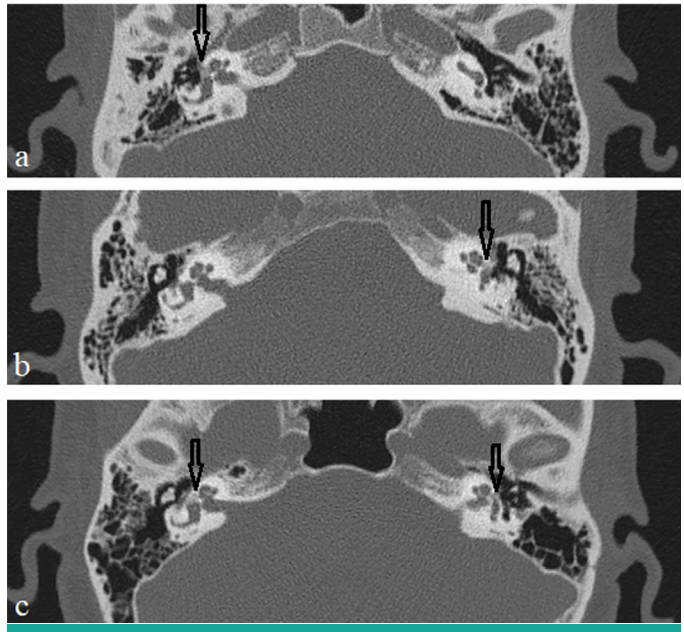

Figure 2. (a) Right fenestral otosclerosis in a 27-year-old female patient (black arrow), (b) Left fenestral otosclerosis is evident in a 27-year-old male patient (black arrow). Bilateral otosclerosis is observed in a 55-year-old female patient (black arrows)

movement, especially that of the stapes, potentially leading to fixation and stress on the stapes footplate, as seen in fenestral otosclerosis. Abnormal alignment of middle ear structures can increase mechanical stress on the stapes, promoting progressive bone remodeling. Temporal bone dimensions, particularly around the otic capsule and cochlea, may affect blood flow and metabolism, and restricted venous drainage can create hypoxia, stimulating abnormal bone remodeling in otosclerosis. Structural differences in the fissula ante fenestram due to abnormal temporal bone dimensions may also increase susceptibility to otosclerosis. A significant narrowing of the dimensions of the facial canal and cochlear aqueduct suggests that these structures are associated with otosclerosis and that anatomical variations may play a crucial role in its pathogenesis (9). The primary objective of the current study was to determine whether temporal bone dimensions are associated with the development of fenestral otosclerosis. Additionally, the relationship between otosclerosis and the presence of a high jugular bulb and jugular bulb dehiscence was evaluated.

Materials and Methods

The current retrospective study was conducted with the approval of the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinical Research Ethics Committee (date: 22.12.2023/file number: 2023/12/09/086), and informed consent was waived due to the retrospective design of the study. The study included a total of 68 subjects with 34 patients radiologically diagnosed with fenestral otosclerosis aged between 41 and 55 years, alongside a control group of 34 healthy subjects matched for age and gender. The inclusion criteria for the patient cohort were a radiologic diagnosis of fenestral otosclerosis and an age of over 18 years. The exclusion criteria for both groups were the presence of retrofenestral otosclerosis, external otitis, otitis media, inner ear abnormalities, tumoral mass, history of otic surgery, semicircular canal dehiscence, and motion artifacts that could compromise diagnostic accuracy. Temporal bone high-resolution computed tomography (HRCT) images collected between January 2023 and January 2024 from subjects included in the study were retrieved from the local Picture Archiving and Communication Systems and transferred to the workstation. The data were retrospectively evaluated using the Syngo.via Siemens program. HRCT examinations were performed without the use of contrast media using a 128-detector sequenced multislice scanner (Ingenuity, Philips, Amsterdam, Netherlands). The imaging parameters were as follows: tube voltage: 120 kV; tube current: 783 mAs; slice thickness: 0.625 mm; field of view: 200; matrix: 768×768; pitch: 0.25 and rotation time: 0.42 s. The images were evaluated by two radiologists in the bone window with a window width of 4095 HU and window level of 600 HU at the workstation, enabling multiplanar reformatted images.

The axial plane was angled to align precisely with the cochlear aperture and bony orbital roof, resulting in a consistent slice orientation, as reported in previous studies in which the temporal bone was examined (Figure 3) (10). Measurements were performed by two board-certified radiologists who reached consensus. A total of 136 temporal bones from the 68 individuals were examined in the axial view that displayed the basal turn of the cochlea at its maximum length, corresponding to the defined standardized axial plane or running parallel to it (Figure 4). The following parameters were recorded: a. The length of the petrous bone from the apex to the external base at its maximum extent is aligned parallel to the primary orientation of the basal turn of the cochlea. The width of the petrous bone centered on the cochlea and perpendicular to the length of the basal turn of the cochlea at its maximum, c. The angle is formed by the length of petrous bone and the midsagittal line. The presence of high-riding jugular bulbs and jugular bulb dehiscence was also noted along with the sides affected.

Statistical Analysis

Data entry and statistical analysis were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). The suitability of data for normal distribution was assessed using both visual (histograms and probability plots) and analytical methods (Shapiro-Wilk test). Numerical data were evaluated using means, standard deviations, and medians (interquartile range 1st-3rd); frequency distributions and percentages were used for summarizing categorical data. Non-normally distributed numerical data were analyzed using the Mann-Whitney U test.

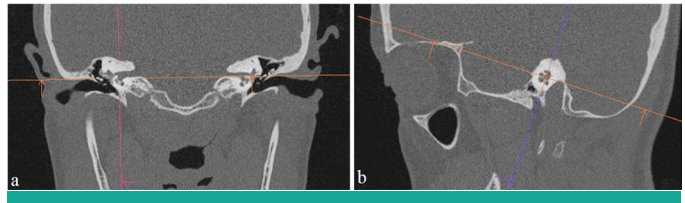

Figure 3. Observation of the bilateral scutum, Prussak's space, and ossicles in the coronal plane shifted the examination to the sagittal plane where a line connecting the cochlear aperture and the orbital roof was drawn. This line provides a guide for further axial assessments

The Pearson chi-square test was used to compare categorical data. Statistical significance was considered at $p<0.05$.

Results

The study cohort comprised 68 participants who were evenly divided into two groups: 34 patients diagnosed with fenestral otosclerosis and 34 age- and sex-matched healthy subjects. The average age of the participants was 48.08±11.23 years, with 44 (64.7%) males and 24 (35.3%) females. The distribution of otosclerosis were as follows: bilateral in 15 (44.1%) patients, left-sided in 11 (32.4%) patients, and right-sided in 8 (23.5%) patients.

High jugular bulbs were present in 55.9% of patients with fenestral otosclerosis and 50.0% of healthy individuals (p=0.627). Among patients with fenestral otosclerosis who had a high jugular bulb, 47.4% had a right jugular bulb, 21.1% had a left jugular bulb, and 31.6% had a bilateral bulb. In the healthy group with a high jugular bulb, 58.8% were found on the right, 29.4% on the left, and 11.8% were bilateral. Jugular bulb dehiscence was observed in 20.6% of patients with fenestral otosclerosis and 23.5% of healthy subjects (p=0.770). Among the patients with jugular bulb dehiscence, 85.7% had it on the right side and 14.3% on the left. In the healthy group, 75.0% of individuals presented with jugular bulb dehiscence on the right, 12.5% on the left, and 12.5% bilaterally (Table 1).

The measurements of petrous bone length, width, and angle were similar for the right and left sides in both the patient and healthy groups (p>0.05) (Table 2). A comparison of the measurements of petrous bone length, width, and angle on the affected sides of patients with the corresponding sides of the controls, as well as on both right and left sides, showed no significant differences between the patient and healthy groups (Table 3).

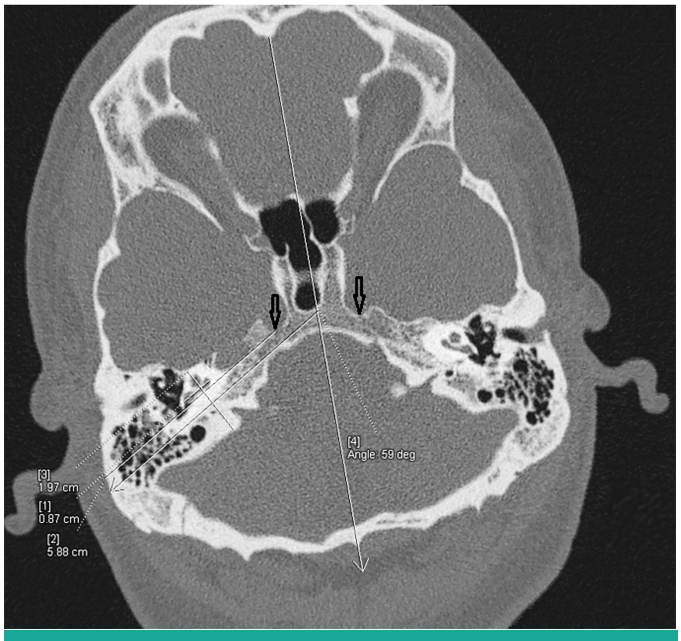

Figure 4. Measurements in the specified axial plane at the workstation using pre-optimized parameters. A line parallel to the cochlear basal turn, as indicated by [1], served as the reference for measuring the length of the petrous bone from the apex to the external base at its maximum extent, as shown in [2] (the petrous apex is indicated by a black arrow at its most medial point). Additionally, [3] the width of the petrous bone, centered on the cochlea and perpendicular to the length of the cochlea's basal turn at its maximum, and [4] the angle formed by the length of the petrous bone and the midsagittal line were measured

Discussion

Hearing loss can substantially diminish the quality of life because of challenges in adaptation and increased social isolation. One of the prevalent causes of hearing loss is otosclerosis, a disease that primarily targets the bony labyrinth of the ear. The pathological changes typically commence near the fissula ante fenestram and subsequently spread via the vascular canals to other parts of the temporal bone. Although there are no definitive data on the etiology or factors that may predispose individuals to otosclerosis, the literature is full of studies that aim to better understand the underlying mechanisms and potential risk factors associated with the development of the disease. Drabkin et al. (11) demonstrated that a *SMARCA4* mutation that causes human otosclerosis produces a

Table 1. Comparison of the prevalence of high jugular bulb and jugular bulb dehiscence between patients and healthy controls

Feature		Patient group (n=34)	Control group (n=34)	p*
		n (%)	n (%)	
High jugular bulb	Present	19 (55.9)	17 (50.0)	0.627
	Absent	15 (44.1)	17 (50.0)	
Side affected by a high jugular bulb (n=36)	Right	9 (47.4)	10 (58.8)	
	Left	4 (21.1)	5 (29.4)	-
	Bilateral	6 (31.6)	2 (11.8)	
Jugular bulb dehiscence	Present	7 (20.6)	8 (23.5)	0.770
	Absent	27 (79.4)	26 (76.5)	
Side affected by jugular bulb dehiscence (n=15)	Right	6 (85.7)	6 (75.0)	
	Left	1 (14.3)	1 (12.5)	-
	Bilateral	-	1 (12.5)	

*: Pearson's chi-square test

Table 2. Comparison of right and left side measurements of petrous bone between the patient and control groups

Measurements	Patient group (n=34)	Control group (n=34)	p*
	Mean ± SD Median (1st-3rd quartile)	Mean ± SD Median (1st-3rd quartile)	
Petrous bone length, R (mm)	63.32±5.04 63.20 (59.45-66.45)	62.89±5.34 63.25 (58.35-67.55)	0.849
Petrous bone width R (mm)	19.42±2.62 19.15 (18.07-20.75)	19.35±3.11 19.70 (17.42-21.42)	0.907
Petrous bone angle, R (°)	53.26±5.47 55.00 (49.00-57.00)	53.23±4.88 54.00 (49.75-56,25)	0.768
Petrous bone length L (mm)	62.11±4.70 61.15 (59.15-64.42)	62.44±4.84 62.50 (58.67-67.02)	0.690
Petrous bone width L (mm)	19.63±2.30 19.35 (18.17-20.40)	19.27±2.94 19.05 (16.75-20.80)	0.611
Petrous bone angle L (°)	53.38±4.41 54.00 (48.75-55.25)	52.26±4.53 52.00 (48.75-56.25)	0.844

*: Mann-Whitney U test, SD: Standard deviation, R: Right, L: Left

Table 3. Comparison of measurements of petrous bone between the affected and healthy sides

Measurements	Patient group	Control group	p*
	Mean ± SD Median (1st-3rd quartile)	Mean ± SD Median (1st-3rd quartile)	
Petrous bone length R (mm) (n=23)	62.92±5.45 61.20 (59.00-65.20)	63.25±4.96 64.00 (59.20-67.50)	0.775
Petrous bone width R (mm) (n=23)	19.41±3.03 17.60 (21.50)	19.13±3.22 18.70 (17.70-21.60)	0.886
Petrous bone angle, R (°) (n=23)	53.82±5.81 55.00 (50.00-58.00)	53.65±4.56 54.00 (50.00-56.00)	0.636
Petrous bone length L (mm) (n=26)	619.8±4.48 61.55 (60.00-64.15)	62.43±4.86 62.50 (58.75-66.85)	0.687
Petrous bone width L (mm) (n=26)	19.49±2.12 19.35 (18.17-20.32)	19.45±2.90 19.05 (17.22-20.80)	0.985
Petrous bone angle (°) (n=26)	52.60±4.48 54.00 (49.00-56.00)	52.53±4.64 53.00 (48.75-57.00)	0.979

*: Mann-Whitney U test, SD: Standard deviation, R: Right, L: Left

similar phenotype in mice, highlighting the critical role of genetic factors. Moss (7) demonstrated the relationship between measles and otosclerosis, illustrating the impact of infections on the etiology of the disease and suggested that viral exposure could influence its pathogenesis. Horner (8) suggested that hormone replacement therapies, specifically those combining estrogen and progestin, may increase the risk of developing otosclerosis and associated vestibular disorders. The same study also noted that hyperprolactinemia may similarly elevate the risk of otosclerosis, thereby highlighting hormonal influence as a significant factor in its etiology.

The relationship between otosclerosis and various anatomical factors has also been extensively studied, yielding significant findings that further our understanding of the complexities involved in the etiology of the disease. A high jugular bulb may exert pressure on middle ear structures, affecting sound transmission and potentially leading to stapes fixation and abnormal bone remodeling in otosclerosis. This condition may impair venous drainage, causing hypoxia or metabolic disturbances that could trigger or worsen otosclerosis. Additionally, disrupting the inner ear anatomy may contribute to sensorineural hearing loss, and mechanical irritation or altered fluid dynamics may lead to inflammation or immune responses, thereby influencing otosclerosis development. Gillet et al. (12) showed that alterations in the stapes footplate can be observed in otosclerosis. The stapes footplate was found to be thickened in patients when examined using only the stapes axial plane. Other studies have revealed a complex array of anatomical factors beyond just the thickening of the stapes footplate. These include significant narrowing

of the facial canal and cochlear aqueduct, among other structural abnormalities, as reported by Cakmak and Cakmak (9). These studies underscore the multifaceted nature of otosclerosis and the need for a comprehensive understanding of the impact of its anatomical features. Friedmann et al. reported no relationship between high jugular bulb and otosclerosis. Building on their findings, our research additionally demonstrated that there was no association between dehiscence of the jugular bulb and otosclerosis, identifying an additional anatomical factor that does not influence the condition (13). Additionally, the current study also investigated the anatomy of the petrous bone as a potential factor in the etiology of otosclerosis. Paetz et al. (10) previously approached the length and width of petrous bone from a developmental perspective. Building upon this, we investigated whether there were any differences in these parameters between patients with otosclerosis and healthy controls; however, we did not find any significant correlation. Lloyd et al. (14) examined the developmental aspects of petrous bone angle. Based on this study, we investigated petrous bone angle in patients with otosclerosis; however, we could not identify any statistically significant differences between the patient and control groups.

The etiology of otosclerosis is multifactorial and has not been fully elucidated. A number of factors can be implicated, including anatomical factors. In the current study, we examined the potential correlation between otosclerosis and anatomical factors, such as a high-riding jugular bulb and its dehiscence. Our study contributes to the existing literature by confirming and reinforcing previous findings of the lack of a significant relationship between otosclerosis and the high-riding status of the jugular bulb. Additionally, we confirmed the absence of any association with jugular bulb dehiscence. We also investigated the potential association between otosclerosis and temporal bone anatomy. Using established measurements from prior studies, we compared the length, width, and angle of petrous bone among cohorts of both healthy individuals and those affected by otosclerosis. We not only compared the measurements between the patient and control groups bilaterally but also the affected sides of patients with the corresponding sides of healthy controls. Nonetheless, statistical analyses revealed no significant differences between the two groups, suggesting that the anatomical dimensions of the petrous part of the temporal bone are not associated with otosclerosis.

Conclusion

Anatomical features such as the dimensions of the facial canal and cochlear aqueduct have been implicated in the etiology of otosclerosis. Previous studies have identified anatomical features, such as a high-riding jugular bulb, which are not significantly associated with the disease. In the current study, we aimed to conduct further anatomical investigations by examining the relationship between jugular bulb dehiscence and otosclerosis; however, our data indicated no significant correlation. Additionally, we performed a comprehensive analysis of the length, width, and angle of the petrous part of the temporal bone and observed no association with otosclerosis compared with healthy controls. These findings indicate that although certain anatomical structures are linked to otosclerosis, others do not contribute to its pathogenesis. Future studies should delve deeper into both the associated and non-associated anatomical factors of otosclerosis to advance our understanding of its etiology.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinical Research Ethics Committee of (date: 22.12.2023/file number: 2023/12/09/086). The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 2000.

Informed Consent: Informed consent was waived due to the retrospective study design.

Footnotes

Authorship Contributions

Concept: E.C., Design: E.C., Data Collection or Processing: M.C. Analysis or Interpretation: E.C. Literature Research: M.C. Writing: E.C., M.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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REVIEW

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Hemodilution and Role of Aquaporins

Hemodilüsyon ve Aquaporinlerin Rolü

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Abstract

This article focuses on the nuanced interplay between hemodilution and aquaporin, elucidating their collective role in preserving fluid homeostasis within the human body. Hemodilution, which is characterized by a reduction in blood component concentration owing to increased plasma volume, commonly occurs during intravenous fluid administration. Aquaporins, integral transmembrane proteins, facilitate water movement across cell membranes. Hemodilution alters osmotic pressure, influencing fluid balance in tissues. Aquaporins, acting as selective water channels, respond dynamically to these changes to ensure precise cellular hydration. This integrated system prevents cellular dehydration and overhydration in the presence of shifting blood volume. Understanding this relationship is clinically significant, especially in fluid-intensive interventions. Healthcare practitioners must consider the potential effects on cellular hydration and osmoregulation, particularly in patients with underlying conditions affecting water homeostasis. Recognizing the intricate connection between hemodilution and aquaporin provides a foundation for optimizing fluid balance in clinical practice. Further exploration of this nexus could lead to the refinement of therapeutic approaches aimed at maintaining cellular integrity and function.

Keywords: Aquaporin, cell membrane, fluid shift, hemodilution, homeostasis

Öz

Bu makale, hemodilüsyon ve akuaporinler arasındaki etkileşimi inceleyerek bunların insan vücudundaki sıvı homeostazisinin korunmasındaki kolektif rolünü açıklamaktadır. Artan plazma hacmi nedeniyle kan bileşeni konsantrasyonunun azalmasıyla karakterize hemodilüsyon, genellikle intravenöz sıvı uygulaması sırasında ortaya çıkar. Aynı zamanda, entegre transmembran proteinleri olan akuaporinler, suyun hücre zarları boyunca hareketini kolaylaştırır. Hemodilüsyon, ozmotik basınçta değişikliklere neden olarak dokulardaki sıvı dengesini etkiler. Seçici su kanalları görevi gören akuaporinler bu değişikliklere dinamik olarak yanıt vererek hassas bir şekilde hücresel hidrasyonu sağlar. Bu entegre sistem, değişen kan hacimleri karşısında hücresel dehidrasyonu veya aşırı hidrasyonu önler. Bu ilişkinin anlaşılması, özellikle yoğun sıvı müdahalelerinde klinik önem taşır. Sağlık uygulayıcıları, özellikle su homeostazisini etkileyen altta yatan sorunları olan hastalarda, hücresel hidrasyon ve osmoregülasyon üzerindeki potansiyel etkileri dikkate almalıdır. Hemodilüsyon ve akuaporinler arasındaki karmaşık bağlantının tanınması, klinik uygulamada sıvı dengesinin optimize edilmesi için bir temel sağlar. Bu bağlantının daha fazla araştırılması, hücresel bütünlüğü ve işlevi sürdürmeyi amaçlayan terapötik yaklaşımların geliştirilmesi için umut vaat etmektedir.

Anahtar kelimeler: Akuaporinler, hemodilüsyon, homeostazis, hücre zarı, sıvı değişimleri

Introduction

Fluid homeostasis is a fundamental aspect of physiological equilibrium and is orchestrated by intricate mechanisms that regulate the composition and volume of bodily fluids (1). One notable phenomenon influencing this delicate balance is hemodilution, a condition characterized by a reduction in the concentration of blood components, primarily driven by an increase in plasma volume (2). Hemodilution commonly occurs in clinical settings, particularly during intravenous fluid administration, raising questions about its impact on the broader context of fluid homeostasis (3).

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Concurrently, aquaporin, a family of transmembrane proteins, play a pivotal role in the dynamic regulation of water movement across cell membranes (4) (Figure 1, Table 1). As integral components of cellular osmoregulation, aquaporin respond to changes in osmotic pressure to maintain optimal cellular hydration (5). The relationship between hemodilution and aquaporin is a crucial nexus in understanding how the body adapts to alterations in blood volume and fluid composition (6). This knowledge holds significant clinical relevance, especially in the context of medical interventions involving fluid administration, as it underscores the importance of considering both hemodilution and aquaporin function for optimal patient care (7).

In this article, we aimed to present the complex interaction between hemodilution and aquaporin and their contribution to fluid homeostasis.

Materials and Methods

This study meticulously conducted a comprehensive literature review, aiming to elucidate the intricate relationship between hemodilution and aquaporin. The methodology prioritized the inclusion of articles published within the substantial timeframe from 2010 to 2024, ensuring a thorough incorporation of the most recent and relevant research findings. Electronic databases, such as PubMed, MEDLINE, and Google Scholar, were systematically searched using a well-defined set of keywords, including "hemodilution", "aquaporins", "fluid homeostasis", and "cellular hydration".

The inclusion criteria were stringent, encompassing only peer-reviewed articles, reviews, and meta-analyses written in English. The selected studies underwent a rigorous evaluation process, considering their methodological robustness, relevance to the research question, and

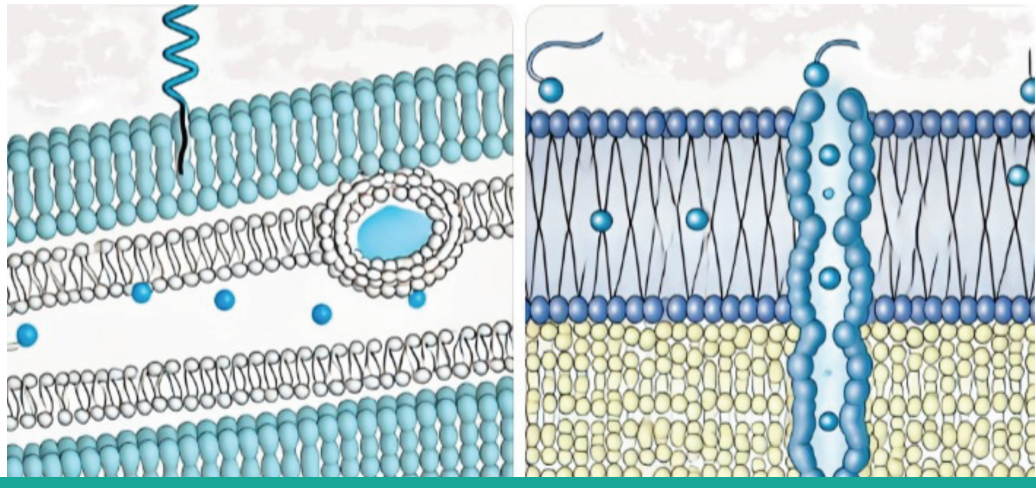

Figure 1. Structure of aquaporins in cell membranes

Table 1. Aquaporin distribution in organs

Aquaporin (AQP) type	Organs/tissues	Functions
AQP1	Kidneys, brain, lungs, eyes, red blood cells	Water transport, osmotic balance maintenance
AQP2	Kidney collecting ducts	Water reabsorption regulated by antidiuretic hormone
AQP3	Kidneys, skin, eyes, lungs	Water and glycerol transport
AQP4	Brain, spinal cord, retina, stomach	Regulates brain and cerebrospinal fluid balance
AQP5	Salivary glands, lacrimal glands, lungs	Water secretion, exocrine functions
AQP6	Kidneys	Water transport in acidic environments
AQP7	Adipose tissue, pancreas, kidneys	Glycerol and water transport
AQP8	Testis, liver, colon	Transport of water and small molecules
AQP9	Liver, spleen, lungs, lymph nodes	Transport of water and other molecules
AQP10	Small intestine	Water and glycerol transport, involved in nutrient absorption
AQP11	Kidneys, liver	Involved in kidney function and possibly small molecule transport
AQP12	Pancreas	Potential role in pancreatic function, still under research

incorporation of contemporary research methodologies. This encompassed studies exploring the molecular and cellular mechanisms underlying hemodilution and aquaporin function, with a focus on understanding their implications for fluid balance across various physiological and clinical contexts.

Data extraction involved a meticulous analysis of experimental designs, methodologies, and key findings, and the identification of any gaps or inconsistencies in the literature. The critical appraisal of selected articles aimed to synthesize a nuanced understanding of the dynamic interconnection between hemodilution and aquaporin, integrating the latest advancements and perspectives in the field.

Recognizing the inherent limitations of relying on existing literature, this study aimed to provide a thorough and up-to-date overview of the current state of knowledge on the subject. The explicit inclusion of studies from the last decade ensures that the findings are not only rooted in established literature but also reflective of the most recent advancements, providing a robust foundation for exploring the multifaceted relationship between hemodilution and aquaporin.

Results

An initial database search identified approximately 62 articles related to hemodilution and aquaporin. Of these, 15 were randomized controlled trials, and 8 were meta-analyses. The remaining studies were observational, reviews, and experimental studies related to hemodilution and aquaporin. After applying the inclusion criteria, 39 studies were reviewed in detail for relevance to fluid homeostasis, aquaporin, and cellular hydration mechanisms.

Temporal dynamics of aquaporin expression (8): An intriguing aspect that emerged from the review was the temporal dynamics of aquaporin expression following hemodilution. Longitudinal studies have provided evidence of time-dependent shifts in aquaporin levels, suggesting an adaptive response that evolves over hours to days. These temporal nuances of aquaporin regulation have implications for the timing of interventions aimed at modulating fluid balance.

Cross-species comparisons: Some studies have ventured into cross-species comparisons, examining the conservation or divergence of hemodilution-aquaporin interactions among different organisms (9,10). Comparative analyses encompassing human studies, animal models, and *in vitro* experiments have enriched our understanding of evolutionary aspects and identified potential translational implications.

Technological advances in aquaporin research: The results highlighted the integration of cutting-edge technologies in aquaporin research. Advanced molecular biology techniques, including *CRISPR/Cas9* gene editing and single-cell RNA sequencing, have enabled a deeper exploration of the intricacies of aquaporin regulation at the genetic and transcriptomic levels (11). These technological advances have paved the way for more precise and targeted investigations (12).

Interactive network analyses (13,14): Network analyses elucidated the interactive relationships between aquaporin and other cellular components. Protein-protein interaction networks and pathway analyses reveal potential downstream effectors and signaling cascades influenced by aquaporin activity. This systems biology approach provides a holistic perspective on the broader cellular response to hemodilution.

Ethnic and geographical variances (15): Sub-analyses considering ethnic and geographical variances offered insights into potential regional disparities in the hemodilution-aquaporin relationship. Variations in genetic predispositions and environmental factors were explored, emphasizing the importance of considering population-specific factors in understanding fluid homeostasis (16).

Emerging biomarkers: Some studies identified potential aquaporin-related biomarkers associated with hemodilution (17). The exploration of these biomarkers holds promise for developing non-invasive diagnostic tools or monitoring strategies for conditions characterized by altered blood volume, providing clinicians with valuable indicators of cellular hydration status (18).

In conclusion, the expansive results of this comprehensive literature review underscore the multifaceted nature of the hemodilution-aquaporin interplay. Beyond molecular mechanisms and clinical implications, the findings traverse temporal dynamics, cross-species considerations, technological advancements, interactive networks, and ethnic variances (8,11,13,15,16,18). These nuanced insights provide a foundation for a holistic understanding of fluid homeostasis and inspire a myriad of directions for future research and clinical applications.

Discussion

The clinical implications of the hemodilution-aquaporin interplay discussed in this review resonate with those of

previous studies on targeted therapeutic interventions (19). Understanding the effects of blood volume alterations on aquaporin function provides a foundation for developing precise treatment strategies (20). This approach aligns with emerging paradigms in personalized medicine, where interventions are tailored based on the molecular intricacies of individual patients (21).

The integration of the findings from this review into fluid management strategies is consistent with ongoing discussions in critical care and perioperative medicine (22). The nuanced understanding of aquaporin dynamics in response to hemodilution offers potential insights for optimizing fluid resuscitation protocols (23,24). These considerations may be particularly relevant in scenarios in which maintaining adequate cellular hydration is paramount for patient outcomes (25).

The comparative effectiveness research aspect of this review, particularly considering the temporal dynamics and cross-species variations, contributes to the evolving landscape of translational medicine (26). Integrating knowledge from diverse sources allows for a more comprehensive evaluation of the effectiveness of interventions in different contexts. This finding aligns with current efforts to bridge the gap between bench research and clinical applications (27).

The integration of findings from this review with concepts from physiology, immunology, and molecular biology highlights the interdisciplinary nature of fluid homeostasis research. The discussion on the inflammatory processes intertwined with hemodilution and aquaporin regulation underscores the need for collaborative efforts across scientific disciplines. This multidisciplinary approach mirrors contemporary scientific inquiry trends that recognize the interconnectedness of physiological systems.

The consideration of ethnic and geographical variances underscores the importance of a global perspective on population health (15,18). Acknowledging the impact of demographic factors on the hemodilution-aquaporin relationship is crucial for developing public health strategies that account for diverse populations. This aligns with a broader movement toward health equity and inclusive healthcare practices.

Although the review provides substantial insights, it also reveals challenges and gaps in our current understanding. The complexities of the hemodilution-aquaporin interplay call for continued exploration, emphasizing the need for more longitudinal studies, standardized methodologies, and deeper exploration of specific aquaporin isoforms. Future research could investigate the functional consequences of altered aquaporin expression under various pathological conditions associated with hemodilution.

The consideration of ethnic and geographical differences also prompts discussion of the importance of global research collaborations. Collaborative efforts across regions can provide a more comprehensive understanding of the hemodilution-aquaporin relationship in diverse populations. This collaborative approach aligns with the increasingly interconnected nature of scientific research, where insights from different parts of the world contribute to a more holistic understanding.

Conclusion

With the findings obtained from this literature review, we conclude that aquaporin, which play a role in fluid homeostasis, are also functional in hemodilution formation owing to their physiological effects.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.E., S.E., Concept: K.E., Design: K.E., Data Collection or Processing: S.E., Analysis or Interpretation: K.E., Literature Search: S.E., Writing: K.E., S.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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REVIEW

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What has Changed in Renal Replacement Treatments?

Renal Replasman Tedavilerinde Neler Değişti?

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Abstract

In the intensive care unit (ICU), acute kidney injury (AKI) is a common and serious complication that significantly affects patient prognosis. High incidence in the ICU is correlated with increased mortality rates. Approximately 50% of ICU patients develop AKI, and 13.5% require renal replacement therapy (RRT). Continuous RRT (CRRT) is particularly beneficial for hemodynamically unstable patients, aiding in dialysis and correction of fluid-electrolyte imbalances, and is effective for patients on vasopressors.

The primary RRT modalities currently in use are the following:

1. Intermittent hemodialysis,

2. Peritoneal dialysis,

3. Slow low-efficiency daily dialysis,

4. CRRTs.

Intiating CRRT in patients with AKI helps prevent uremia and sudden death from renal failure complications. Despite the presumed significance of the timing, modality, and dosing of CRRT on clinical outcomes, research in this area is limited, thereby rendering the role of CRRT in AKI management controversial.

Initiating CRRT involves selecting an appropriate device and method, choosing a suitable catheter and filter, and determining blood flow and ultrafiltration rates. This review discusses the emergency indications for CRRT, definitions of RRT modalities, CRRT program implementation, CRRT prescription, management including blood flow rate and solutions, complications, anticoagulation strategies, prevention of clotting issues, citrate accumulation, contraindications, RRT in sepsis guidelines, and nutritional aspects.

As a result, considering the scarcity of reviews written on this subject, we aimed to present a practical approach by adding the missing topics on this subject and supporting topics, such as dose calculations and anticoagulation management, with current literature in the light of practical applications.

Keywords: Acute renal failure, critical care, continuous kidney support therapy

Öz

Akut böbrek hasarı (AKI); yoğun bakım hastalarında prognozu etkileyen yaygın bir komplikasyondur. Yoğun bakımda görülme sıklığı yüksek ve mortalite ile ilişkilidir. Yoğun bakım hastalarının yaklaşık %50'sinde AKI görülür. AKI görülen hastaların, %13,5'i renal replasman tedavisine (RRT) ihtiyaç duyar. Hemodinamik olarak stabil olmayan hastalarda sürekli renal replasman tedavisi (CRRT), sıvı-elektrolit dengesinin düzeltilmesinde yardımcı olmakla kalmaz, aynı zamanda vazopressör kullananlar için de etkili bir tedavi görevi görür.

Günümüzde yaygın olarak kullanılan dört ana RRT türü vardır:

1. Standart hemodiyaliz,

2. Periton diyalizi,

3. Yavaş, düşük akımlı günlük diyaliz,

4. CRRT.

AKI olan hastalarda CRRT başlanması, böbrek yetmezliği komplikasyonlarından üremi ve ani ölümü önleyebilir. CRRT'nin zamanlaması, modaliteleri ve doz ayarlamalarının klinik sonuçlar üzerinde etkisine rağmen bu konudaki çalışmalar sınırlıdır. Bu nedenle CRRT'nin AKI yönetimindeki rolü tartışmalı olmaya devam etmektedir.

CRRT'yi başlatırken özel adımlar izlenmelidir. Öncelikle uygun cihaz seçilmeli, hastaya en uygun yöntem belirlenmelidir. Kan akış hızı ve ultrafiltrasyon hızının belirlenmesiyle birlikte filtrasyon için uygun kateter ve filtre seçilmelidir.

Bu derlemede sürekli renal replasman tedavisinin acil endikasyonları, RRT yönteminin tanımı, CRRT programlarının uygulanması, CRRT reçetesi, kan akış hızı ve çözümleri dahil yönetim, komplikasyonlar, antikoagülasyon stratejileri, pıhtılaşma sorunlarının önlenmesi, sitrat birikimi ve kontrendikasyonları tartışılmaktadır.

Sonuç olarak bu konuda yazılan derlemelerin az olması gözönüne alınarak biz de bu konuda eksik olan konu başlıklarını ekleyip pratik uygulamalar ışığında doz hesaplamaları, antikoagülasyon yönetimi gibi konular güncel literatürlerle destekleyerek pratik yaklaşımı sunmayı hedefledik.

Anahtar kelimeler: Akut böbrek hasarı, sürekli renal replasman tedavisi, yoğun bakım

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Introduction

Acute kidney injury (AKI) is a common complication that adversely affects the prognosis of intensive care unit (ICU) patients. The incidence of AKI in the ICU is high and is associated with increased mortality. AKI has various etiologies; while some patients have known risk factors. However, the inflammatory response associated with critical illness can also trigger AKI. Non-renal factors, such as nephrotoxic drugs, hypoxia, hypovolemia, and arterial hypotension, also contribute to AKI pathogenesis (1,2). Approximately 50% of ICU patients develop AKI, with 13.5% requiring renal replacement therapy (RRT) (3). Continuous RRT (CRRT) is particularly beneficial for hemodynamically unstable patients, facilitating dialysis and correction of fluid-electrolyte imbalances, and is effective for patients on vasopressors (4).

The purpose of this review was to describe how to effectively use RRT in acute renal failure, which is common in ICUs and has a high mortality rate. Which method should be used when and where, emergency indications, definition of the RRT method, implementation of CRRT programs, CRRT prescription, blood flow rate, and solutions. The management, complications, anticoagulation strategies, prevention of clotting problems, citrate accumulation, and contraindications are discussed.

The primary RRT modalities currently in use are the following:

1. Intermittent hemodialysis (HD)

2. Peritoneal dialysis (PD)

3. Slow low-efficiency daily dialysis (SLED)

4. CRRTs

Intermittent HD is optimal for patients with hemodynamically stable condition, with bicarbonate used as the buffer. This procedure requires a skilled team, specialized instruments, and well-functioning vascular access. It is preferred for rapid solute, fluid, and toxins removal. Advances in HD devices and the availability of appropriately sized equipment (vascular access, dialyzer, etc.) are significant (5).

1. HD

Kinetic indicators:

• Urea reduction rate (URR): URR = (Upre - Upost/Upre) x 100. The minimum URR should be 65-70%.

• Kt/V: Used to show air conditioning.

• K: Urea clearance of the dialyzer (mL/min)

• t: Dialysis time (min)

• V: Urea distribution volume (mL)

• For adequate HD, the Kt/V should be >1.4. CRRT administration is not calculated.

2. Peritoneal Dialysis (PD)

PD purifies blood from harmful substances and removes excess fluid using the patient's peritoneum as the dialysis membrane. Special solutions are infused into the peritoneal cavity through a permanent silicone catheter placed during minor surgery. PD does not require vascular access and is favored for its simplicity and ease of use without special training. It maintains critical hemodynamic balance, eliminating dialysis-related hypotension and urea decrease syndrome. PD does not require anticoagulation, is cost-effective, and does not necessitate detailed equipment. However, PD is not suitable for every patient. Rapid solute (hyperkalemia), toxin, and metabolite (ammonia) clearance may be insufficient in PD. The presence of a ventriculoperitoneal shunt is a partial contraindication to PD (6).

3. Slow Low-efficiency Daily Dialysis (SLED)

SLED (7) is a "hybrid" therapy combining features of both intermittent and CRRT. SLED sessions last 6-12 hours, with blood flow rates generally between 100 and 300 mL/minute. For dialysate, water from a wall outlet or appropriate electrolytes and sterile water is used.

Advantages of SLED:

• Reduced need for anticoagulation due to shorter sessions.

• Patient inactivity for much of the day.

• Better hemodynamic tolerance.

• Lower cost compared with CRRT, and no need for anticoagulation.

Drawbacks of SLED:

• Less effective than ischemic heart disease .

• May not be tolerated by extremely disturbed or unstable patients.

• No mortality difference between different RRT methods, so no survival advantage, but increased comfort and reduced cost (8).

4. Description of CRRT and Methods

In patients with AKI, the initiation of CRRT is crucial for preventing uremia and sudden death associated with renal failure. Although variations in the timing, modalities, and dosing of CRRT are believed to influence clinical outcomes, particularly survival, few studies have examined this topic. Thus, the role of CRRT in the management of AKI remains a subject of debate (9).

Certain procedural steps must be adhered to during the initiation of CRRT. First, an appropriate CRRT device must be selected, followed by the determination of the most suitable method for the patient. Subsequently, a suitable catheter and an appropriate filter for filtration are selected. Blood flow and ultrafiltration rates must also be determined (10).

The selection and rate adjustment of dialysate or replacement fluid are critical, and anticoagulation management is necessary to prevent clotting. In conclusion, CRRT in AKI effectively prevents uremia and sudden death. However, no definitive guidance has been provided on the optimal timing for CRRT initiation, and further research on this topic is required (10).

The efficacy of RRT in patients with severe metabolic acidosis due to lactic acidosis remains controversial, as the clearance rate provided by RRT is significantly lower than the endogenous generation rate (11). Although RRT is frequently used as supportive treatment and acts as a bridge to definitive treatment of the underlying cause of lactic acidosis (e.g., bowel resection for ischemic bowel), limited evidence supports its mortality benefit. An exception is the treatment of metformin-associated lactic acidosis, in which RRT can effectively reverse the underlying cause.

Patients who are oliguric or maintain a persistent positive fluid balance despite high-dose loop diuretics (often used in conjunction with thiazide or thiazide-like diuretics), especially if their oxygen requirements are increasing, may benefit from elective RRT initiation. This treatment can help avoid the need for intubation and mechanical ventilation (12).

Indications for urgent initiation of RRT in AKI (13-15).

The criteria necessitating prompt initiation of RRT in AKI patients often include the following:

• Fluid overload resistant to diuretic therapy.

• Severe hyperkalemia (plasma potassium >6.5 mEq/L) or rapidly escalating potassium levels.

• Signs of uremia like pericarditis, encephalopathy, or unexplained deterioration in cognitive function.

• Severe metabolic acidosis unresponsive to medical interventions (pH <7.1); though the effectiveness of RRT for lactic acidosis is uncertain.

• Specific alcohol and drug poisonings suitable for extracorporeal therapy.

In individuals with pre-existing chronic kidney disease, the need for RRT is associated with the extent of baseline glomerular filtration rate reduction (10). Other factors to consider include.

• Serum potassium levels of >6.0 mEq/L not improved with aggressive medical management, or >5.5 mEq/L accompanied by ongoing tissue damage (e.g., rhabdomyolysis, crush injury, tumor lysis syndrome) or compromised potassium excretion.

Severe metabolic acidosis (pH <7.15) that persists without reversible causes despite optimal medical management (e.g., intravenous sodium bicarbonate therapy, if volume status allows). The decision to start RRT is not solely based on a specific pH value; some experts suggest considering RRT initiation at higher pH levels (e.g., pH <7.2) (16).

Initiating RRT early in AKI before the appearance of urgent or elective signs usually does not offer advantages and might hinder renal recovery and increase healthcare utilization. Studies comparing early and delayed RRT initiation indicate that factors like fluid overload, hyperkalemia, acidosis, and uremia should determine when to start RRT (16).

Many studies have compared strategies for early initiation of RRT (in the absence of any indications mentioned above) with delayed initiation of RRT (after indications have developed) (11,16,17). The best data come from a large, multicenter, randomized study and a previously published meta-analysis that synthesizes findings from older, smaller studies. Specific indications include fluid overload, hyperkalemia, acidemia, and uremia. In most institutions, intermittent HD is the standard RRT method for haemodynamically stable patients (18). According to clinical practice patterns, CRRT is the main indication for intermittent HD. Hypotension is believed to be less common in CRRT (although it may occur) because fluid and solute removal rates are slower than those in intermittent HD (19).

Intermittent HD is commonly used as the standard RRT method in most facilities for patients who are hemodynamically stable. Continuous CRRT is preferred for hemodynamically unstable patients because of the

perceived lower risk of hypotension, although randomized trials have not consistently shown superior hemodynamic stability or survival over intermittent HD (19-21). Optimal strategies for fluid removal in critically ill patients have yet to be defined (22). CRRT is particularly advantageous for patients with acute brain injury or conditions causing increased intracranial pressure because it minimizes hemodynamic fluctuations that could exacerbate cerebral edema compared with intermittent HD (23).

CRRT may also be preferred over intermittent HD for conditions such as sepsis, burns with extensive fluid loss, heart failure, and liver failure (2). However, intermittent HD is generally favored over CRRT for severe hyperkalemia associated with electrocardiogram change refractory to medical therapy, particularly if vasopressors are required.

Definition of RRT Modalities (24,25)

Various CRRT modalities differ primarily in their mechanisms of solute transport, which include diffusion and/or convection.

Diffusion: This process involves the movement of solutes across a semi-permeable membrane driven by concentration gradients. Dialysis fluid creates a diffusion gradient, with blood and dialysate flowing in opposite directions to maximize the concentration differences. Standard HD predominantly relies on diffusion, with some contribution from convection.

Convection: This method filters plasma water through a membrane under hydrostatic pressure, facilitating the transport of small and medium molecular weight solutes along with water. A replacement fluid is used to maintain an adequate plasma volume and enhance solute removal. Convection is integral to hemofiltration, allowing solute movement through hydrostatic pressure gradients. No single CRRT method has demonstrated superior efficacy.

Adsorption: This involves the retention of solutes by binding to the membrane, and it is particularly effective for large molecular weight substances and certain inflammatory cytokines.

Ultrafiltration: This process involves the removal of water from semi-permeable membranes driven by pressure gradients (hydrostatic, osmotic, or oncotic). The latest CRRT methods use venovenous circuits in which blood is routed by an extracorporeal blood pump through a dialyzer or hemofilter. Double-lumen intravenous H is universally required. Arteriovenous methods based on the interval between temperature arterial pressure and venous pressure are no longer used because of the arterial method packages.

Commonly used CRRT methods: Continuous ventricular hemodialysis (CVVHD) is primarily removed by diffusion. Dialysis fluid is run at 1-2 L/h against the direction of blood flow, with an ultrafiltration rate typically ranging from 2 to 8 mL/min (23). The dialysate blood flow rate was 20-25 mL/kg/hour. In the CVVHD system, ultrafiltration is limited to the desired net fluid removal rate; replacement fluid is not required.

Continuous venovenous hemofiltration (CVVH): This technique achieves solute removal through convective clearance. The blood passes through a porous membrane, allowing ultrafiltration. The ultrafiltrate was replaced with a pre- or post-filter replacement fluid. Small and medium-sized molecules are removed by convection, maintaining their concentration in the vascular space. The ultrafiltration rate typically ranges from 20 to 25 mL/kg/hour (26). Hydrostatic pressure drives plasma water filtration across the hemofilter membrane, removing solutes exclusively by convection. Unlike dialysis fluid, the replacement fluid adjusts the plasma volume without significantly altering the solute concentration. Predilution with a replacement fluid can enhance urea removal by lowering its plasma concentration, thereby allowing diffusion from red blood cells into plasma water (27,28).

Continuous ventricular hemodialysis (CVVHD): In this method, the dialysis solution flows in the opposite direction to the blood flow around the dialysis membrane, providing diffusive clearance via concentration gradients. Sterile and physiological dialysate are used. Dialysate content provides a concentration gradient that allows solute removal. The permeability coefficient of low-molecular-weight substances is close to 1, facilitating their removal at a similar rate by convective and diffusive clearance. The permeability coefficient of medium- and large-molecular-weight substances is lower, and their clearance is more efficient with the convective method (29).

Continuous venovenous hemofiltration (CVVHDF): This modality combines diffusion with convection and is the preferred method in intensive care patients with multiorgan failure and advanced heart failure. CVVHDF requires the infusion of both replacement fluid and dialysis fluid. The ultrafiltration volume varies, and replacement fluid must be administered to maintain euvolemia. The amount of

fluid to be administered was determined by subtracting the desired net volume.

Slow continuous ultrafiltration (SCUF): Also known as isolated ultrafiltration, SCUF is a simple fluid removal method that produces isotonic ultrafiltrate. This method can remove 3-6 liters of fluid and, due to slow ultrafiltration, does not cause significant hemodynamic disturbances or hypotension, minimizing the negative effects on the kidneys, lungs, and heart. In intensive care patients, particularly those with pulmonary edema, heart failure, sepsis, or acute respiratory distress, slow excretion of excess fluid effectively regulates cardiac output, tissue oxygenation, and mean blood pressure. SCUF is used therapeutically in patients with fluid overload but is not useful in uremic or hyperkalemic patients because of minimal solute removal. It can safely remove up to a maximum of 8 L of fluid per day. Neither replacement fluid nor dialysis fluid is used (4,30).

CRRT is a complex intervention to address critical problems and requires involvement not only by critical care services but also by nephrology, formality, pharmacy, and nutritional support systems, and coordination across many disciplines is required (30).

CRRT Program Model

Each hospital is recommended to follow a registered protocol outlined by an expert panel. This protocol covers the provision of vascular support and CRRT prescription, including anticoagulation, CRRT module, dose, and CRRT solutions. The standardization processes of these decisions will be increased, and the quality will increase. Additionally, improvement and monitoring of CRRT quality indicators that track outcomes, such as survival of CRRT circuits, minor solute clearance, bleeding events, interruptions, and interruptions (i.e., the time during which treatment of CRRT is not delivered), are supported. Although there is no conclusive evidence on the performance of such follow-up programs in improving patient problems, data suggest that they increase the specificity of CRRT (31,32).

Vascular access: CRRF requires vascular access that can supply a blood flow rate of 200-250 mL/min 26. Optimal vascular access is important for ensuring CRRT circuit function; CRRT performance is impaired when suboptimal access is used. The insertion sites, catheter size, configuration, length, and depth, and insertion techniques are outlined. Deeper catheters that may be inserted into larger central veins or the abdominal inferior vena cava could improve CRRT circuit performance and are thus preferred. Therefore, a catheter that can be inserted into the right atrium or veno-atrial junction of the inferior vena cava (33). Although some practitioners use unique triple-lumen dialysis catheters for CRRT, these catheters are not as popular in general due to the smaller internal diameter of the two dialysis lumens, which may compromise blood flow. A third lumen (in the case of a triple-lumened catheter) should not be utilized for life-saving medications (such as anti-microbials), during CRRT therapy and should only be reserved for drugs that do not present a risk due to drug clearance by CRRT (33).

Hemofilter: Size and membrane structure are considered in CRRT filters. If the blood is filtered through larger-area filters, filtration fractions are higher and hemoconcentration probabilities are lower. This, however can slow the flow rate of blood within the filter (if it is too big). The filter material is usually a hollow fiber or flat plate membrane with polyacrylonitrile (not acrylic, the plastic) structures.

The filter material typically consists of microtubules or plate-shaped membranes composed of polyacrylonitrile [AN-69, AN69 surface treated (ST)], polysulfone, or polyaryletersulfone (PAES). Filter selection options should be based on weight and specific clinical indication. In the CRRT method, biocompatible membranes with high permeability, amplification, and flux are used. Common membrane materials include polyacrylonitrile (AN69), PAES, and polyethersulfone (34).

There is no conclusive evidence showing the superiority of one membrane type over another. Theoretically, due to their negative charge, polyacrylonitrile membranes can enhance the adsorption and removal of medium-molecular-weight particles such as cytokines. However, no significant difference was observed in the results. Polyacrylonitrile membranes can cause the release of bradykinin; therefore, this agent should not be used in patients with untreated AN69 membranes or in recent or angiotensin-converting inhibitor use due to reported cases of anaphylaxis (35). However, AN69 ST membranes, which are coated with a polycationic solution to reduce surface electronegativity and prevent bradykinin formation, can be safely used with these drugs.

Filter priming: Prior to treatment, air must be removed from the filter, which should be filled with a balanced solution (usually 0.9% NaCl. Before the procedure, 2-5 units/kg of heparin should be added to the 0.9% NaCl solution. In patients with bleeding tendency, the initial wash can be performed with heparinized 0.9% NaCl, followed by a wash with plain 0.9% NaCl. For hemodynamically unstable patients, the filter can be primed with 5% albumin or blood.

CRRT prescription: CRRT prescription includes selection of the CRRT method, anticoagulation strategy (if used), filtration fraction, blood flow, dose, CRRT replacement or dialysis solution, and fluid removal procedures.

CRRT method: CRRT methods include CVVH, CVVHD, and CVVHDF. These mixtures differ in that they do not move away from the solute: CVVH convection can be used, CVVHD diffusion can be used, and CVVHDF combines both convection and diffusion. The filtration fraction, defined as the fraction of plasma water that enters the dialyzer and is removed by ultrafiltration (convection) across the dialysis membrane, operates below 20 percent. 20% higher filtration fraction may increase circuit coagulation due to hemoconcentration and blood protein-membrane transitions inside the hemofilter (36).

CRRT blood flow rate: A blood flow rate of 100-200 mL/min is often used for anticoagulation medications. In patients not receiving anticoagulation, a higher blood flow rate (250 to 300 mL/min) may be used to maintain battery patency and longevity after CRRT. However, a randomized study showed no difference in the amount of circuit failure between blood flow rates of 150 and 250 mL/min (37). When the blood circulation, hematocrit (Hct), and total wastewater flow rates are constant, purely convective treatment modes (such as CVVH) have a higher utilization fraction than diffusion treatments.

Key definitions and abbreviations of CRRT (38)

• **Ultrafiltrate:** Volume of plasma removed from circulating blood.

• **Dialysate:** Fluid flowing inside the filter in the direction opposite to blood flow.

• **Replacement fluid:** Fluid provided before and after the filter to compensate for the removed ultrafiltrate.

• **Qb:** Blood flow rate (100-300 mL/min).

• **Qd:** Dialysis fluid flow rate (usually 1-3 L/H).

• **Qr:** Rate of replacement fluid administered to compensate for fluid loss through solute excretion in convection applications.

• **Qnet:** Net fluid removed from the patient every hour.

• **Quf:** Ultrafiltration rate, defined as Qr + Qnet.

• **CVVH:** Continuous venovenous hemofiltration with no dialysate and only replacement fluid. Quf = Qr + Qnet.

• **CVVHD:** Continuous venovenous hemodialysis with dialysate fluid but no replacement fluid. Quf = Qd + Qnet.

• **CVVHDF:** Continuous venovenous hemodiafiltration with both dialysate fluid and replacement fluid. Quf = Qd + Qr + Qnet.

Example calculation

For a patient weighing 70 kg, the following parameters were used:

• Prefilter replacement fluid: 1000 mL/h

• Postfilter replacement fluid: 400 mL/h

• Dialysate flow rate: 800 mL/h

• Fluid removed from the patient: 200 mL/h

Effluent calculation: Effluent = prefilter + postfilter + dialysate + fluid removed = 1000+400+800+200=2400 mL/h

To calculate the effluent dose: 2400 mL/h/70 kg =34.2 mL/kg/h

For patients using prefilter replacement fluid, the effluent dose decreases because of blood dilution: Plasma flow rate (mL/h) = blood flow rate (mL/min) × 60 min/h × (1 - Hct) Plasma flow rate = 150×60×(1 - 0.3) =6300 mL/h

Dilution factor = Plasma flow rate / (Plasma flow rate + prefilter replacement dose) Dilution factor =6300/(6300+1000)=0.86

Actual effluent: Actual effluent = Effluent × dilution factor Actual effluent =34.2×0.86 =29.4 mL/kg/h

The patient's actual effluent value will be 29.4 mL/kg/h.

Filtration Fraction

The filtration fraction (FF) is defined as FF = Ultrafiltration flow rate/Plasma water flow rate

Plasma water flow rate = Blood flow rate × (1 - Hct) + prefilter replacement fluid flow rate + any other pre-pump infusion rate (such as citrate).

For example, if the blood flow is set to 100 mL/min and postfilter replacement fluid is set at 2000 mL/h in a patient undergoing CVVH: Blood passes through the filter at 100 mL/min and is excreted as ultrafiltrate at 2000/60=33 mL/min. Thus, 67 mL of 100 mL of plasma remained at the filter outlet. With a Hct of 30%, the Hct concentration will increase to 44.7% at the filter outlet, resulting in higher coagulation risk and filter clogging.

To calculate FF in this scenario: Ultrafiltration rate (Quf) = 2000 mL/h or 33 mL/min FF = Quf / Qb (1 - Hct) = 33/100 (1-0.3) =0.47 FF =47%, which is above the desired level of 25%. To mitigate this effect, increasing the blood flow to 200 mL/min reduced the FF to 23%.

CRRT Dose

Key definitions and abbreviations of CRRT (39)

• **Ultrafiltrate:** Volume of plasma extracted from circulating blood.

• **Dialysate:** Fluid flowing inside the filter in the direction opposite to blood flow.

• **Replacement fluid:** The fluid was administered before and after the filter to compensate for the removed ultrafiltrate.

• **Qb:** Blood flow rate (100-300 mL/min).

• **Qd:** Dialysis fluid flow rate (usually 1-3 L/H).

• **Qr:** Rate of replacement fluid administered to compensate for fluid loss through solute excretion in convection applications.

• **Qnet:** Net fluid removed from the patient every hour.

• **Quf:** Ultrafiltration rate, defined as Qr + Qnet.

• **CVVH:** Continuous venovenous hemofiltration with no dialysate and only replacement fluid. Quf = Qr + Qnet.

• **CVVHD:** Continuous venovenous hemodialysis with dialysate fluid but no replacement fluid. Quf = Qd + Qnet.

• **CVVHDF**: Continuous venovenous hemodiafiltration with both dialysate fluid and replacement fluid. Quf = Qd + Qr + Qnet.

Example calculation

For a patient weighing 70 kg, the following parameters (40).

• Prefilter replacement fluid: 1000 mL/h

• Postfilter replacement fluid: 400 mL/h

• Dialysate flow rate: 800 mL/h

• Fluid removed from the patient: 200 mL/h

Effluent calculation: Effluent = prefilter + postfilter + dialysate + fluid removed = 1000+400+800+200=2400 mL/h

To calculate the effluent dose: 2400 mL/h/70 kg =34.2 mL/kg/h

For patients using prefilter replacement fluid, the effluent dose decreases because of blood dilution: Plasma flow rate (mL/h) = blood flow rate (mL/min) × 60 min/h × (1 - Hct) Plasma flow rate = 150×60×(1-0.3) = 6300 mL/h

Dilution factor = Plasma flow rate / (Plasma flow rate + prefilter replacement dose) Dilution factor =6300/(6300+1000)=0.86

Actual effluent: Actual effluent = Effluent × dilution factor Actual effluent =34.2×0.86=29.4 mL/kg/h

The patient's actual effluent value will be 29.4 mL/kg/h.

Maintaining a low-filtration fraction A low-filtration fraction can be achieved by

• Low ultrafiltration flow rate

• It is necessary to increase the blood flow rate and improve catheter function.

The low filtration fraction can be achieved by

• Keeping the ultrafiltration flow (convection) rate low.

• Increasing the blood flow rate while ensuring that catheter function can support higher flows.

• Pre-filter replacement fluid in CVVH or CVVHDF.

A crucial component of CRRT prescription is the "dose" or the dialysate/replacement fluid flow rate. Unlike intermittent dialysis, which is based on the Kt/V, CRRT is prescribed in liters per hour. No definitive CRRT dose has been determined to provide superior outcomes. Early observational studies suggested that higher CRRT doses improved mortality rates (41), prompting clinicians to prescribe doses up to 35 mL/kg/h. However, subsequent large randomized studies [the acute tubular necrosis (ATN) study and the RENAL study] found no clinical benefit of high-dose CRRT compared with doses of 20-25 mL/kg/h (42,43). Consequently, the CRRT dose is typically set at 20-25 mL/kg/h.

Most studies continued CRRT for 24 h. If treatment cannot be continuously maintained for 24 hours, the fluid output should be increased to achieve the target dose of 20-25 mL/kg/hour. In most studies, the dose was reported as the hourly volume of total dialysate or replacement fluid. For each hour during which treatment is stopped, the dose for that hour is zero. Generally, CRRT aims to improve patient outcomes in regenerative medicine. When treatment is halted or the circuit malfunctions, the target dose is achieved by initiating a new CRRT circuit or dialysis treatment.

The filtration fraction has an inverse relationship with blood flow. Therefore, low blood flow rates (less than 100 to 150 mL/min) can lead to hemofilter and circuit problems due to blood stasis and a higher filtration fraction. Conversely, higher blood flow rates (above 250 to 300 mL/min) might reduce circuit lifespan if the vascular

access cannot sustain these high rates for long periods. Poor catheter performance can result in increased pressure alarms, temporary stoppage of the blood pump, blood stasis, and more frequent circuit clotting.

Solute Clearance and Blood Flow Rate: Variations in blood flow rates between 100 and 300 mL/min typically do not affect solute clearance. Solute clearance can be limited by either the blood or waste flow rate. Because the blood flow rate usually exceeds the waste flow rate, solute clearance is often constrained by the waste flow rate, except when the waste flow rate matches or exceeds the blood flow rate. For CVVHD, the blood flow rate should be at least 2.5 times the dialysate flow rate to fully saturate the dialysate and maintain the correlation between dialysate velocity and solute clearance. In the CVVH with post-filter replacement fluid, the blood flow rate should be at least 5 times the exchange fluid rate to optimize the filtration fraction. With the prefilter replacement fluid in the CVVH, the blood flow rate should be at least 6 times the exchange fluid rate to enhance solute clearance. In patients anticoagulated with regional citrate anticoagulation (RCA), higher blood flow increases the citrate requirement, thereby increasing the cost and risk of complications because more citrate enters the systemic circulation.

Lastly, the blood flow rate did not affect the hemodynamic stability because the volume of blood in the circuit remained constant at any given rate.

CRRT Solutions (44-46)

Sodium

• The sodium concentration in commercial solutions ranges from 130 to 140 mEq/L.

• The physiological sodium concentration (135-140 mEq/L) is appropriate for most patients.

• In patients receiving citrate anticoagulation therapy, lower sodium (130 mEq/L) can prevent hypernatremia.

Potassium

• The potassium concentration in standard solutions ranged from 0 to 4 mEq/L.

• A potassium concentration of 4 mEq/L is used in patients without severe hyperkalemia.

• Solutions containing 0 or 2 mEq/L potassium can be used to treat severe hyperkalemia.

Bicarbonate

• Bicarbonate-based solutions are preferred over lactate-based solutions.

• The bicarbonate concentration in standard solutions ranged from 22 to 35 mEq/L.

• A bicarbonate concentration of 22-25 mEq/L was used in patients treated with RCA, and 32-35 mEq/L in other patients.

• The appropriate bicarbonate concentration should be adjusted to prevent metabolic alkalosis, a common side effect of RCA.

Phosphate (47,48)

Standard solutions: Standard solutions for CRRT either do not contain phosphorus or contain 1 mmol/L phosphorus. A phosphorus-containing solution is indicated for patients with serum phosphate levels <4.5 mg/dL, whereas a solution lacking phosphorus is utilized for patients with higher phosphate levels.

Glucose

Standard solutions: CRRT solutions can be glucose-free or containing 100-110 mg/dL glucose. Glucose-free solutions are preferred for hyperglycemic patients; however, there is an inherent risk of hypoglycemia and euglycemic diabetic ketoacidosis associated with their use.

Calcium

Standard solutions: CRRT solutions may either be calcium-free or contain 2.5-3.5 mEq/L calcium. In the context of RCA, calcium-free solutions are generally preferred to mitigate the risk of calcium precipitation and other complications.

Fluid Removal (48,49)

Target: A net negative fluid balance of 150-200 mL per hour is standard practice. It is crucial to monitor the patient's hemodynamic status continually; adjustments to the fluid removal rate should be made in response to signs of fluid intolerance.

Laboratory Monitoring

Monitoring protocol: Electrolyte levels and acid-base status should be monitored initially every 6-12 hours. After patient stabilization, the frequency of monitoring can be extended to every 12-24 hours. More frequent monitoring is warranted when RCA is used.

Complications

Complications of CRRT: CRRT is associated with a range of potential complications, including electrolyte imbalance, mineral disturbance, acid-base disorders, hypotension, infections, bleeding, and hypothermia (50). One notable but often unrecognized complication is subtherapeutic

antibiotic concentrations, which necessitates careful adjustment of antimicrobial dosing regimens in patients undergoing CRRT.

The most frequent complications are hypophosphatemia, hypokalemia, and hypomagnesemia (51). The closer the electrolyte concentrations in CRRT solutions are to physiological levels, the less need for additional replacement therapy.

1. Hypophosphatemia,

2. Hypokalemia,

3. Alkalosis: Patients receiving citrate anticoagulation may develop metabolic alkalosis or metabolic acidosis (52). In patients with normal liver function and muscle perfusion, metabolic alkalosis is observed, facilitating the conversion of systemic citrate to bicarbonate. Metabolic acidosis may occur in acute liver failure or severe shock in which citrate metabolism is impaired (53).

4. Hypomagnesemia: A frequent complication of CRRT that can be managed through intravenous magnesium administration. Some clinicians may also incorporate magnesium into CRRT.

5. Hypernatremia: A risk in patients with RCA if the CRRT solution contains standard sodium concentrations (e.g., 140 mEq/L). In such cases, a solution with a reduced sodium concentration of 130 mEq/L is preferred.

6. Hypocalcemia: Less commonly, calcium or hypocalcemia may occur when citrate is used for anticoagulation or in dialysis or fluid replacement. Abnormalities following citrate anticoagulation therapy are corrected by careful adjustment of calcium infusion.

7. Hypotension: Although CRRT is less frequent than intermittent HD (23), hypotension remains a significant concern, with incidence rates comparable between CRRT and HD in some studies (35% vs. 39%, respectively) (53). Ultrafiltration rate is a key determinant of hypotension risk, particularly in patients with diabetic neuropathy, reduced ventricular ejection fraction, diastolic dysfunction, or sepsis. Continuous monitoring of the patient's clinical status and hemodynamic stability is essential for adjusting the ultrafiltration rate to prevent or manage hypotension.

8. Hypothermia: Prolonged circulation of blood in the extracorporeal circulation can induce hypothermia (54). Hypothermia occurred in 17% of patients undergoing CRRT compared with 5% in those receiving intermittent HD. Hypothermia may obscure the detection of fever, and preventive measures include using blood warmers or external heating devices (54).

9. Infection and bleeding: Infection and bleeding are known complications associated with opening an RRT dialysis catheter.

Current Anticoagulation

Anticoagulation options: The primary anticoagulation methods for CRRT include RCA and unfractionated heparin (UFH) (55). Although less common, include low molecular weight heparins (LMWH), thrombin antagonists, protamine-reversible heparinoid, nafamostat mesilate, platelet-inhibiting agents, and heparin-coated hemofilters.

Regional citrate anticoagulation (RCA): RCA is an effective anticoagulation strategy applicable to all CRRT modalities (56-58). Compared with systemic heparin, RCA has a lower risk of bleeding (59,60). In RCA, sodium citrate is administered into the arterial line of the extracorporeal circuit to chelate calcium ions and prevent clot formation. The majority of citrate-calcium complexes are removed by the hemofilter, and the remaining citrate is metabolized to bicarbonate by the liver, kidneys, and muscles. Additional calcium infusion is required to maintain normal ionized calcium levels. Adjustments in the composition of dialysate or replacement fluids may be necessary during RCA, and increased buffer concentrations (e.g., bicarbonate, lactate) should be carefully managed to prevent alkalosis. Dialysate or replacement fluid containing 0.75 mmoL/L magnesium is preferred over 0.5 mmol/L because of citrate's binding effect on magnesium (61).

Unfractionated heparin (UFH): UFH remains a prevalent anticoagulation option for CRRT (62), especially in scenarios where RCA is not available. Although UFH is effective, cost-effective, and widely accessible, it has several challenges, including unpredictable pharmacokinetics, the risk of heparin-induced thrombocytopenia, potential heparin resistance in patients with low antithrombin levels, and a higher bleeding risk (51). The incidence of bleeding complications in patients with UFH ranges from 10% to 50% and is often correlated with prolonged activated partial thromboplastin time (aPTT) (63,64).

Other approaches: Alternative anticoagulation methods: Low molecular weight heparins, Thrombin antagonists, nafamostat mesylate, prostacyclin, other prostanoids, and platelet inhibitor regulatory agents (65-67).

Optimizing the CRRT Parameters

Maintaining adequate blood flow: Optimal blood flow rates for CRRT range from 100 to 300 mL/min (68). Flow rates below this range increased the risk of clotting due to stasis and an elevated filtration fraction, whereas flow rates exceeding 300 mL/min triggered alarms and potentially caused stasis or failure of circuit tubing.

Minimizing hemoconcentration: To reduce hemoconcentration:

• Maintain a filtration fraction below 20-25% to minimize circuit clotting (69).

• Discontinued diffusive treatments, such as CVVHD or CVVHDF, over convective treatments like CVVH.

• Mitigate coagulation risks at blood-air interfaces by ensuring proper circuit setup, maintaining a saline layer above the blood in the drip chamber, promptly responding to alarms, minimizing blood-air contact, controlling fluid temperature appropriately, and preventing mechanical blockages in blood lines.

Approach to recurrent hemofilter clotting: RCA is preferred over UFH when available because of the prolonged hemofilter lifespan, reduced bleeding risk, and decreased transfusion requirements (70). UFH is an alternative treatment option when RCA is contraindicated or not tolerated. Here is a revised version with reduced similarity:

Meta-analysis: A comprehensive meta-analysis involving 11 randomized trials and 992 patients (70). compared RCA with systemic heparin (nine studies) and regional heparin (two studies). The findings indicated that RCA had a lower risk of circuit loss compared with both regional and systemic heparin. Additionally, the risk of bleeding was reduced with RCA compared with systemic heparin and was similar to that with regional heparin. There were no significant differences in survival rates between the groups. A report from the UK also found no notable differences in survival between RCA and UFH, with only minor variations in bleeding events (71).

Blood flow rate and RCA: A blood flow rate of 80-200 mL/min is recommended. Higher flow rates, which are typically unnecessary in non-anticoagulated patients to prevent clotting, may increase citrate requirements.

Citrate contraindications: RCA should be avoided in patients with impaired citrate metabolic clearance (72), including:

• **Hyperacute liver failure:** Patients with serum liver transaminases exceeding 1000 international units/L may experience ineffective citrate metabolism, leading to reduced ionized calcium and severe acidosis. RCA should be reconsidered as liver function improves. Patients with acute, subacute, or acute-on-chronic liver failure can often metabolize citrate adequately although the risk of citrate accumulation and hypocalcemia is elevated (73).

• **Cardiogenic shock:** RCA is limited in patients with lactate levels >8 mmol/L because of impaired citrate metabolism. It may be reconsidered with clinical improvement and lactate reduction to ≤8 mmoL/L (74). Some centers adjust citrate infusion rates or increase dialysis clearance for these patients. Monitoring the effectiveness of circuit anticoagulation depends on the citrate delivery method. Fixed-dose citrate with stable blood flow does not require frequent monitoring, whereas variable-dose citrate necessitates post-filter ionized calcium monitoring at least every six hours, with the citrate infusion being adjusted to maintain levels between 0.3 and 0.4 mmol/L (75). Some centers may monitor less frequently (76).

Indications for discontinuation of RCA due to citrate accumulation: RCA should be discontinued if citrate accumulation is detected. It is difficult to predict which patients will develop citrate accumulation. High-risk patients include.

1. Patients with hyperacute liver failure and serum liver transaminase levels >1000 IU/L

2. Those in cardiogenic shock with lactate levels >8 mmol/L

However, other causes of hyperlactatemia do not necessarily contraindicate the use of citrate (77). The symptoms of citrate accumulation include (78-81):

1. Metabolic acidosis with increased anion gap.

2. Decrease in ionized calcium concentration despite high calcium infusion rates.

3. Total increased calcium level.

4. The ratio of total calcium to ionized calcium was >2.5.

There is no exact value for the duration of RCA; instead, trends in these criteria are monitored, and RCA is discontinued only when all criteria are met. Before discontinuing RCA, attempts can be made to reduce citrate accumulation by lowering the dialysate infusion rate in patients undergoing hemodialysis or hemodiafiltration. Avoiding positive calcium balance and overcorrection of

hypocalcemia in patients with severe rhabdomyolysis is crucial.

Other complications: Complications associated with RCA include hypocalcemia, hypercalcemia, hypernatremia, hypomagnesemia, and acid-base imbalances. Although rare, alkalosis or acidosis can develop; these are not typically reasons to stop RRT unless there are signs of citrate accumulation (82). The frequency of complications varies according to the treatment protocol and the patient's health condition. In a study of 133 patients with RCA, approximately 2% experienced severe alkalosis (pH >7.55) and approximately 11% had severe hypocalcemia (ionized calcium ≤0.9 mmoL/L) (83). No cases of hypercalcemia (ionized calcium ≥1.5 mmoL/L) were reported. Alkalosis occurrence is reduced in patients with RCA when replacement and dialysate solutions have lower bicarbonate concentrations, typically 22-25 mEq/L compared with 32-35 mEq/L in non-RCA patients. Severe acidosis can develop if citrate is inadequately metabolized by the liver or muscles although acidosis can also occur without citrate accumulation (84).

Unfractionated Heparin

Anticoagulation with UFH: If RCA is contraindicated and anticoagulation is necessary, UFH is used. The heparin infusion rate is an initial loading dose of 500 to 1000 units followed by a maintenance infusion of 500 units initially. Baseline switching of aPTT or anti-Xa level (aPTTr), limiting target aPTT of 45 seconds or aPTTr to 1.5 times normal (85,86). Patients with disseminated intravascular coagulation and thrombocytopenia should reduce the dose of heparin. The use of heparin-coated dialyzer membranes has not shown significant benefits compared with standard anticoagulation-free protocols (87).

Discontinuing RRT: RRT is typically continued until there is evidence of improved renal function. Increased urine output is the primary indicator of improved renal function in oliguric patients is increased urine output. Improvement in renal function may also be indicated by a progressive decrease in serum creatinine levels despite constant creatinine clearance. A creatinine clearance <12 mL/min is likely insufficient for therapy discontinuation. In the ATN program, RRT was discontinued if the creatinine clearance measured in blood exceeded 20 mL/min. If the flow rate is between 12 and 20 mL/min, it is left to the discretion of the practitioner (43).

Conclusion

Acute renal failure is common in the ICU. RRT is administered to patients with unstable hemodynamics. This issue must be well understood to avoid complications and reduce costs. The most common anticoagulant options for CRRT are UFH, RCA, and no anticoagulant. Less common anticoagulation options include protamine reversal UFH and LMWH. The choice of anticoagulant for CRRT should be based on patient characteristics, local expertise, and the ease of monitoring. The Kidney Disease Improving Global Outcome AKI guidelines recommend using RCA instead of UFH in patients with no contraindications to citrate and those with or without a high risk of bleeding. The evaluation should include an evaluation of the anticoagulant effect, circuit life, filter efficiency, and complications, and we have presented them in detail in this review.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B., E.K., A.P., Concept: B.B., E.K., A.P., Design: B.B., E.K., A.P., Data Collection or Processing: B.B., E.K., A.P., Analysis or Interpretation: B.B., E.K., A.P., Literature Search: B.B., E.K., A.P., Writing: B.B., E.K., A.P.

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CASE REPORT

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Superficial Cervical Plexus Block for Postoperative Pain Management in Patients Undergoing Supraglottic Laryngectomy and Bilateral Neck Dissection: A Case Series

Supraglottik Larenjektomi ve Bilateral Boyun Diseksiyonu Yapılan Hastalarda Postoperatif Ağrı Yönetiminde Yüzeyel Servikal Pleksus Bloğu Uygulaması: Olgu Serisi

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Abstract

Superficial cervical plexus block (SCPB) has been widely utilized in anesthesia and analgesia management for head and neck surgeries. This case series aims to share our experience with SCPB for postoperative analgesia in patients undergoing supraglottic laryngectomy, bilateral neck dissection, and tracheostomy due to laryngeal carcinoma. SCPB was administered to 10 patients aged over 18 years with an ASA score of 2 or 3, who underwent supraglottic laryngectomy, bilateral neck dissection, and tracheostomy between January 15, 2023, and March 15, 2023. The blocks were performed using ultrasonography guidance with 0.1 mL/kg of 0.25% bupivacaine. Routine anesthesia induction was followed by maintenance with 2% sevoflurane and intravenous remifentanil infusion. Postoperative pain was assessed using the numeric rating scale (NRS) at 1, 6, 12, and 24 hours. The average NRS scores were 1.6 at 1 hour, 2.3 at 6 hours, 2.4 at 12 hours, and 2.4 at 24 hours postoperatively. SCPB was effective in reducing postoperative pain, with minimal additional analgesia required. No complications related to SCPB were observed.

SCPB provides effective postoperative pain management for patients undergoing supraglottic laryngectomy and bilateral neck dissection, with a favorable safety profile. However, further studies with larger sample sizes and comparison groups are needed to validate these findings.

Keywords: Cervical plexus block, head and neck surgery, regional anesthesia, tracheostomy

Öz

Süperfisyal servikal pleksus bloğu (SCPB), baş ve boyun cerrahilerinde anestezi ve analjezi yönetiminde yaygın olarak kullanılmaktadır. Bu olgu serisi, larinks karsinomu nedeniyle supraglottik larenjektomi, bilateral boyun diseksiyonu ve trakeostomi uygulanan hastalarda SCPB ile postoperatif analjezi yönetimindeki deneyimlerimizi paylaşmayı amaçlamaktadır. 15 Ocak 2023 ile 15 Mart 2023 tarihleri arasında supraglottik larenjektomi, bilateral boyun diseksiyonu ve trakeostomi yapılan, ASA skoru 2 veya 3 olan 18 yaş üzeri 10 hastaya SCPB uygulandı. Bloklar, ultrasonografi rehberliğinde, %0,25 bupivakainin 0,1 mL/kg'lik dozu ile gerçekleştirildi. Rutin anestezi indüksiyonunu takiben, %2 sevofluran ve intravenöz remifentanil infüzyonu ile idame sağlandı. Postoperatif ağrı, 1, 6, 12 ve 24 saatlerde sayısal derecelendirme skalası (NRS) kullanılarak değerlendirildi. Ortalama NRS skorları postoperatif 1. saatte 1,6, 6. saatte 2,3, 12. saatte 2,4 ve 24. saatte 2,4 olarak kaydedildi. SCPB, postoperatif ağrıyı azaltmada etkili olmuş ve minimal ek analjezi gereksinimi doğmuştur. SCPB ile ilgili herhangi bir komplikasyon gözlenmemiştir. SCPB, supraglottik larenjektomi ve bilateral boyun diseksiyonu geçiren hastalarda etkili postoperatif ağrı yönetimi sağlamaktadır ve güvenli bir profil sunmaktadır. Ancak, bu bulguların doğrulanması için daha büyük hasta grupları ve karşılaştırma gruplarını içeren çalışmalar gerekmektedir.

Anahtar kelimeler: Baş ve boyun cerrahisi, rejyonel anestezi, servikal pleksus bloğu, trakeostomi

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Introduction

Superficial cervical plexus block (SCPB) is a safe and useful alternative to general endotracheal anesthesia for surgery of the neck, upper shoulder, and occipital scalp area (1,2). Over the subsequent years, it has become a widely used technique in the anesthesia and analgesia management of head and neck surgeries (3). In this letter, we aim to share our experience with SCPB for analgesia management in 10 patients who underwent supraglottic laryngectomy, bilateral neck dissection, and tracheostomy due to laryngeal carcinoma.

Case Report

Between January 15, 2023, and March 15, 2023, SCPB was administered to 10 patients aged over 18 years with an American Society of Anesthesiologists score of 2 or 3, who underwent supraglottic laryngectomy, bilateral neck dissection, and tracheostomy (Table 1). The indication for surgery in all cases was laryngeal carcinoma, which necessitated the removal of the supraglottic structures, comprehensive neck dissection to address lymphatic spread, and the establishment of a secure airway via tracheostomy. Written informed consent was obtained from all patients.

The blocks were performed in the anesthesia preparation room with the patients under routine monitoring. After administering 0.02 mg/kg midazolam, a high-frequency (12-15 MHz) linear ultrasonography (USG) probe (Hitachi Arietta 65 ultrasound device) was placed transversely at the mid-point of the sternocleidomastoid muscle at the cricoid level. Using the in-plane technique, the prevertebral fascia deep to the sternocleidomastoid muscle was visualized (Figure 1). Following negative aspiration, 0.1 mL/kg of 0.25% bupivacaine was administered with USG guidance to ensure the spread of the local anesthetic (4). The procedure was repeated on the contralateral side. No complications related to the procedure were observed. Importantly, in the bilaterally applied block, the phrenic nerve is preserved, which reduces the risk of diaphragmatic dysfunction and associated respiratory complications.

Each patient received a routine premedication of 2 mg intravenous midazolam. This was followed by 1 mcg/kg fentanyl, 2-3 mg/kg propofol, and 0.6-0.8 mg/kg rocuronium administered intravenously. Maintenance anesthesia was provided with 2% sevoflurane in a mixture of air and oxygen, along with 0.05-0.2 mcg/kg/min intravenous remifentanil infusion.

Routine anesthesia induction and orotracheal intubation were performed. Radial artery cannulation was done for monitoring. At the end of the uncomplicated surgeries, patients received 1 g paracetamol and 100 mg tramadol for analgesia and were extubated with sugammadex. They were then transferred to the intensive care unit (ICU) with tracheostomy, conscious, and breathing spontaneously with 4 L/min oxygen support.

Postoperatively, 1 g of paracetamol was administered at 8, 16, and 24 hours. Pain scores, measured using the numeric rating scale (NRS), are summarized in Table 1. One patient

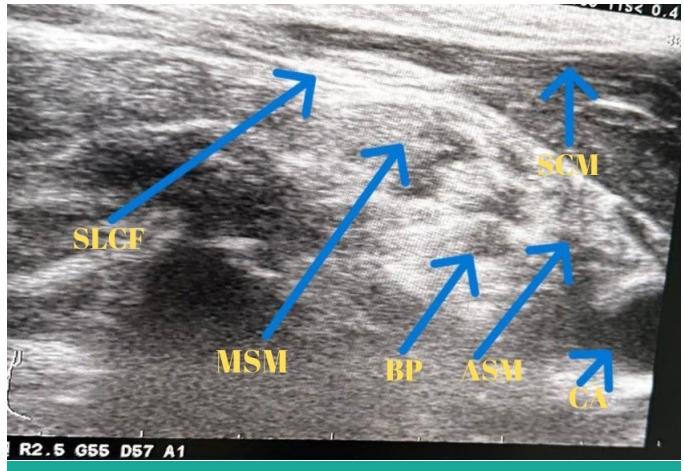

Figure 1. Ultrasonographic view of superficial cervical plexus

SLCF: Superficial layer of cervical fascia, MSM: Middle scalene muscle, ASM: Anterior scalene muscle, CA: Carotis artery, BP: Brachial plexus, SCM: Sternocleidomastoid muscle

Table 1. Demographical data of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	53	62	61	71	68	59	64	62	57	55
Gender	M	F	M	M	M	F	M	M	F	M
BMI	28.1	27.7	22.5	23.9	28.2	29.7	24.1	23.4	28.6	27.9
Comorbidities	0	DM, HT	HT, CAD	DM, HT, KKY	HT	DM, HT	HT	0	HT	0

BMI: Body mass index, DM: Diabates mellitus: CAD: Coronary artery disease, HT: Hypertension

Table 2. Postoperative pain and coughing scores (NRS)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Average
1st hour	2	1	1	1	3	3	1	2	1	1	1.6
6th hour	1	2	1	1	6	4	1	2	3	2	2.3
12th hour	3	2	3	2	2	3	2	2	2	3	2.4
24th hour	3	2	2	1	3	3	3	1	3	3	2.4
Coughing	1	3	2	3	4	1	2	1	2	2	2.1

NRS: Numeric rating scale

with an NRS score of 4 received 75 mg intramuscular diclofenac sodium, and another with an NRS score of 6 received 4 mg intravenous morphine hydrochloride. All patients were transferred to the ward after a 24-hour ICU stay.

The average NRS scores at different postoperative times were as follows; 1 hour: 1.6, 6 hours: 2.3, 12 hours: 2.4, 24 hours: 2.4 (Table 2).

Discussion

Our findings demonstrate that the use of SCPB in patients undergoing supraglottic laryngectomy and bilateral neck dissection for laryngeal carcinoma effectively reduces postoperative pain levels. The average NRS scores at 24 hours follow-up were relatively low, indicating good pain control.

It is important to note that, to the best of our knowledge, this case series represents the only report in the literature that examines the use of SCPB specifically for patients undergoing supraglottic laryngectomy, bilateral neck dissection, and tracheostomy. There are no previous studies that have focused on the efficacy of SCPB in this specific surgical context. However, SCPB has been studied in other types of head and neck surgeries, such as thyroid surgery, where it has been shown to be effective for analgesia. For instance, a systematic review and meta-analysis by Wilson et al. (5) demonstrated the analgesic effects of bilateral SCPB in thyroid surgery, highlighting its potential to reduce pain with a favorable safety profile.

The advantages of SCPB include its ability to provide targeted pain relief without the systemic side effects associated with opioids. This is particularly beneficial in head and neck surgeries where opioid-induced respiratory depression can complicate recovery, especially in patients with a tracheostomy.

Moreover, SCPB was associated with minimal complications in our case series, highlighting its safety profile. The use of USG ensured accurate placement of the local anesthetic, which likely contributed to the efficacy and safety observed.

This study has several limitations. Firstly, the absence of patient-controlled analgesia (PCA) devices in the postoperative pain management protocol may have limited the ability to accurately assess opioid consumption, as PCA allows for precise tracking of opioid usage and provides more personalized pain control. Secondly, the study lacked a comparison group, which restricts the ability to draw definitive conclusions about the efficacy of SCPB relative to other analgesic methods. Lastly, the small sample size of only 10 patients reduces the generalizability of the findings. Future studies with larger sample sizes, comparison groups, and the inclusion of PCA devices are needed to provide more robust evidence for the use of SCPB in this surgical context.

Conclusion

In conclusion, SCPB provides effective postoperative pain management for patients undergoing supraglottic laryngectomy and bilateral neck dissection, offering a viable alternative to opioid-based analgesia.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.S., Ö.A., E.M., F.G.Ö., Concept: O.S., Ö.A., E.M., F.G.Ö., Design: O.S., Ö.A., E.M., F.G.Ö., Data Collection or Processing: O.S., Ö.A., E.M., E.İ.T., F.G.Ö., Analysis or Interpretation: O.S., Ö.A., E.M., E.İ.T., F.G.Ö., Literature Search: O.S., Ö.A., E.M., E.İ.T., F.G.Ö., Writing: O.S., Ö.A., E.M., E.İ.T., F.G.Ö.

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CASE REPORT

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"Spontaneous Subcapsular Hematoma of the Liver Complicating Acute Calculous Cholecystitis": A Rare Case Report and Literature Review

"Akut Taşlı Kolesistiti Komplike Eden Karaciğerin Spontan Supkapsüler Kanaması" Nadir Bir Olgu Sunumu ve Literatürün Değerlendirilmesi

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Abstract

Spontaneous subcapsular liver hematoma is a rare condition, and this case report describes the clinical course of an 85-year-old female patient who developed a spontaneous subcapsular hematoma while being followed up for acute cholecystitis. After exacerbation of right upper-quadrant pain, imaging studies revealed hematoma. The patient was managed conservatively, with subsequent imaging showing a reduction in the size of the hematoma, and her hemodynamic stability was maintained. This case highlights the diagnostic, therapeutic, and clinical considerations of spontaneous subcapsular liver hematoma and provides a broader perspective by comparing it with similar cases in the literature.

Keywords: Hematoma, liver, spontaneous, supcapsular

Öz

Spontan subkapsüler karaciğer kanaması nadir görülen bir durum olup, bu olgu sunumu, akut kolesistit nedeniyle takip edilen ve spontan subkapsüler kanama gelişen 85 yaşındaki bir kadın hastanın klinik seyrini anlatmaktadır. Hastanın sağ üst kadran ağrısının şiddetlenmesi üzerine yapılan tetkiklerde kanama tespit edilmiş, konservatif tedavi ile takip edilen hastada kanama boyutlarında küçülme gözlenmiş ve hemodinamik stabilite korunmuştur. Bu olgu, spontan subkapsüler karaciğer kanamalarının tanısı, tedavi seçenekleri ve klinik seyrinde dikkat edilmesi gereken noktaları vurgulamakta ve literatürdeki benzer olgularla karşılaştırma yaparak konuya geniş bir perspektif sunmaktadır.

Anahtar kelimeler: Hematom, karaciğer, spontan, supkapsüler

Introduction

Spontaneous subcapsular liver hemorrhage is a rare but potentially fatal condition. In most cases reported in the literature, an iatrogenic cause (such as surgical, percutaneous, or endoscopic intervention) or a predisposing factor (such as liver pathologies, pregnancy, trauma, or anticoagulant use (1-5).Herein, we present a case of subcapsular hemorrhage that developed in an 85-year-old female patient with known cholelithiasis and compare it to similar cases described in the literature.

Case Report

An 85-year-old female patient with a history of gallstones for several years presented to the emergency department with complaints of abdominal pain in the right upper quadrant. The patient had a history of coronary artery disease (CAD)

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that was treated with angiography 8 years previously but had no known additional diseases or medications. On examination in the emergency department, the patient presented with pain and tenderness in the right upper quadrant. Intravenous (IV) contrast-enhanced computed tomography (CT) images were consistent with cholecystitis. The patient, who did not want surgery and felt relief with analgesics, was discharged with a prescription for a proton pump inhibitor (PPI), antibiotic (cefuroxime), and analgesic.

Three days later, the patient returned to the emergency department with abdominal pain and vomiting. Because of vomiting, she was unable to take oral antibiotics, and she was admitted to the general surgery department.

On the day of hospitalization, complete blood count, biochemistry, and urinalysis were performed. All values were within normal ranges except for liver function tests and C-reactive protein, an acute-phase reactant. Routine tests and endoscopy were planned.

Following her admission, the infection disease specialist recommended IV clarithromycin (2,500 mg) and IV metronidazole [3,500 mg (due to suspected allergy to cefuroxime)]. Her diet was restricted to fat-free liquid foods. PPI and analgesics were added to her treatment, and IV hydration was maintained. The patient's IV contrast-enhanced CT scan performed at the emergency department did not show any additional pathology except for a hydropic gallbladder and dilated common bile duct (8 mm) (Figure 1).

On the second day of hospitalization, the patient developed sudden severe pain in the epigastric region and right upper quadrant. Physical examination revealed only pain and tenderness upon palpation. On the same day, his hemoglobin level dropped from 14.9 g/dL at admission to 10.5 g/dL (Table 1). The patient appeared more fatigued than on the previous day. New symptoms included burning during and frequent urination. Urinalysis and urine culture were performed, and based on the advice of an infection disease specialist, clarithromycin was discontinued, and the antibiotic was switched to piperacillin/tazobactam. Meanwhile, magnetic resonance cholangiopancreatography performed the previous day to evaluate intra- and extrahepatic bile ducts revealed a fluid collection compatible with subcapsular hemorrhage surrounding the superior and lateral regions of the liver's right and left lobes, approximately 4.5 cm in length. Routine blood tests taken the same day confirmed a drop in hemoglobin levels to 10.5 g/dL.

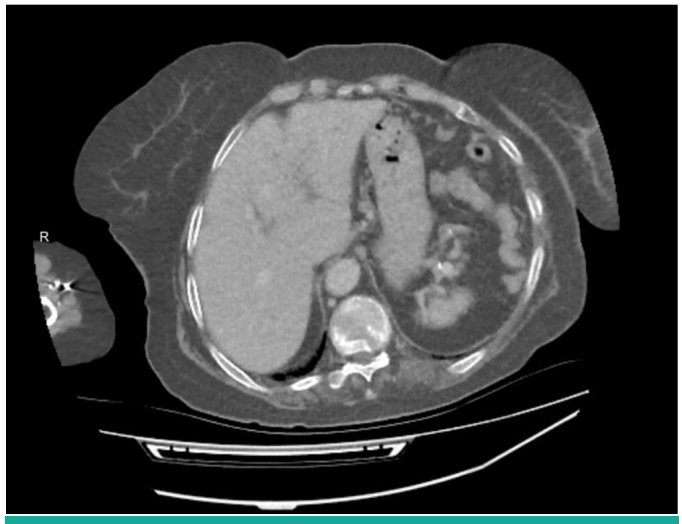

Figure 1. No hemorrhage was observed in the liver on the CT scan performed in the emergency department
CT: Computed tomography

Table 1. Progression of the patient's blood parameters

Blood test	Normal range	Units	Admission	SHH diagnosed	Discharge
HB	11-16	g/dL	14.9	9.5	11.6
WCC	4-10	10^9/L	6.31	8.02	5.21
PLT	100-400	10^3/L	144	133	135
GGTP	6-42	U/L	300	296	157
AST	2-35	U/L	166.4	155.2	29.3
ALT	0-40	U/L	245.2	189.7	24.2
CRP	0-5	mg/L	103.3	68.2	25.06
INR	0.8-1.2	INR	1.05	1.18	1.13
APTT	25.4-36.9	seconds	28.6	23.6	28.5
Thrombin time	10.2-13.9	seconds	12.3	13.8	13.2

SHH: Sonic hedgehog, HB: Hemoglobin, WCC: White cell count, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, INR: International normalized ratio, APTT: Activated partial thromboplastin time

On the third day of hospitalization, after detecting fluid consistent with hemorrhage on magnetic resonance imaging, the patient underwent another evaluation with ultrasonography (USG). The USG showed subcapsular collections measuring 15x5 cm in the dome of the right liver lobe and 6x5 cm in the left lobe, characterized by poorly defined hypoechoic areas with dense content, suggestive of hemorrhage (Figure 2). The patient had no history of trauma, and no signs of hemorrhage were observed in the CT scan taken before admission. By the third day of hospitalization, spontaneous subcapsular hemorrhage had developed, as confirmed by follow-up imaging (Figure 3).

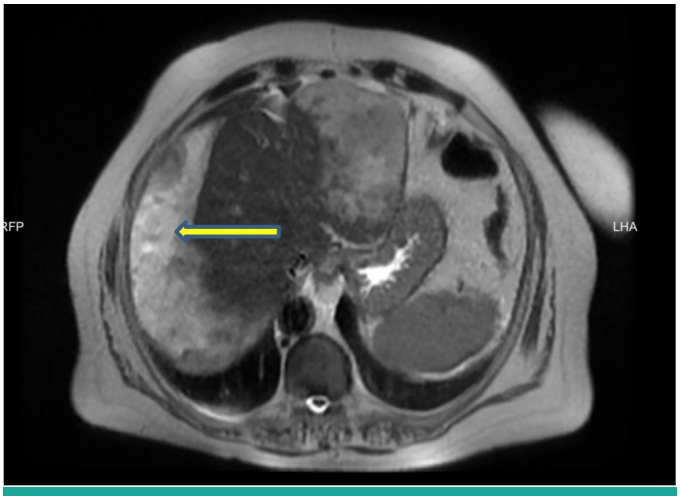

Figure 2. Subcapsular hepatic hematoma detected on MRCP obtained to evaluate extrahepatic bile duct pathology (yellow arrow)

MRCP: Magnetic resonance cholangiopancreatography

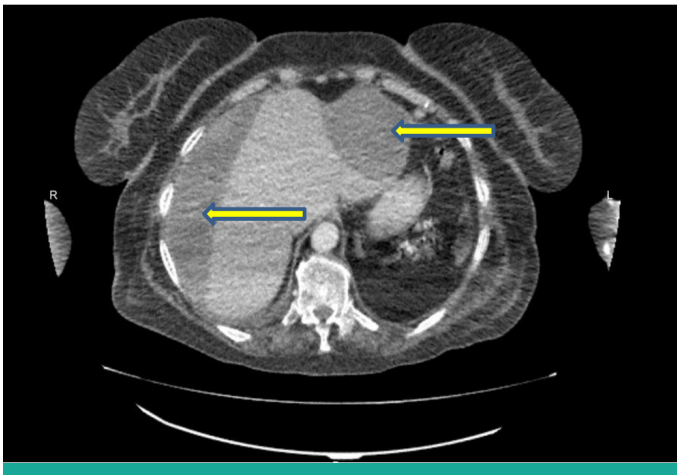

Figure 3. Subcapsular hepatic hematoma on CT scan (yellow arrow)

CT: Computed tomography

Daily follow-up of the patient revealed a decrease in hemoglobin levels by approximately 1 g/dL over 24 hours. On the fourth day of hospitalization, the hemoglobin level was measured to be 8.8 g/dL, after which the patient received two units of erythrocyte suspension and one unit of fresh frozen plasma, raising the hemoglobin level to 10.8 g/dL. No additional pathology was found on endoscopy performed on day 4.

During the hospital follow-up, as the hemorrhage stabilized and hemoglobin levels returned to normal, discharge was planned. The patient was transferred to the pulmonology department due to respiratory distress. Before the patient was transferred to the pulmonary diseases department, a case report was prepared, and informed consent was obtained from the patient and their relatives. During the pulmonologist's follow-up, an USG showed that the hemorrhage had regressed to a size of 5 cm. Approximately 2 months after discharge, the patient was brought to the emergency department because of respiratory failure, where he subsequently experienced respiratory arrest and was declared extubated.

Discussion

Subcapsular hemorrhage of the liver is defined as bleeding between Glisson's capsule and the hepatic parenchyma. There are different underlying causes of liver hemorrhage. It is often described as a complication of preeclampsia during pregnancy (3). Other common causes include liver trauma (4), iatrogenic injuries following endoscopic retrograde cholangiopancreatography (1), biliary tract surgery, and liver biopsy. Liver neoplasms, chronic liver diseases (2), coagulopathic, vasculitis, and anticoagulant medications (5) can also lead to subcapsular hemorrhage.

In this case, we followed an 85-year-old patient who had not used any anticoagulants for several years despite having a history of CAD and was cognitively intact and atraumatic. The clinical presentation of our patient was similar to a case reported by Burrows-O'Donoghue et al. (6), where the patient's age and clinical history were comparable to our case, although their patient was on low-dose anticoagulants (Table 2). Although low-dose anticoagulant use is not expected to cause significant life-threatening hemorrhage, it may still predispose a patient to bleeding.

Our literature review identified eight cases of spontaneous subcapsular hepatic hemorrhage without a clear underlying cause. In addition to our presented case, we evaluated a total of nine patients and found that the average age

was 57.7 years. However, it should be noted that the age distribution of the patients was broad, ranging from 36 to 85 years. Interestingly, 66.6% of the reported cases were female, whereas 33.3% were male.

When examining the clinical course of these cases, we observed that in six of the cases (66.6%), the hemorrhage regressed with supportive care and conservative management, without the need for any interventional procedures or surgical intervention. In only one case reported by Tanaka et al. (11), arterial embolization and percutaneous drainage were required because of sudden hemodynamic deterioration (development of hemorrhagic shock). In the case reported by Malle and Kone(12), surgical intervention was necessary due to rupture of the hematoma capsule. Both patients were discharged following inpatient

Table 2. Summary of reported spontaneous subcapsular liver hemorrhages and a comparison of their clinical courses

	Information	Procedure	Maximum hematoma size	Outcome
Case 1 (7)	81 year-old Male Hipothyroidism Left renal agenesis	Conservative treatment and follow-up	1 cm	Discharge after 3 days of follow-up
Case 2 (8)	40 year-old Male No comorbidities	Conservative treatment and follow-up	16x10x3 cm	Discharge after 1 week of follow-up
Case 3 (9)	36 year-old Female No comorbidities Use of compression garment (Faja)	Conservative treatment and follow-up	13.7x5.6x9.5 cm	Discharge after 1 week of follow-up
Case 4 (6)	79 year-old Female CAD, heart failure, type 2 diabetes, obesity, cholecystitis	Conservative treatment and follow-up	Not specified	Discharge after 1 month of follow-up
Case 5 (10) **(History of recurrent liver hemorrhage)**	52 year-old Female Hypertension Breats cancer (Taking tamoxifen)	Conservative treatment and follow-up (Due to suspicion tamoxifen was discontinued and parasite treatment was initiated)	-13 cm (in segment 8) -8.8 cm (in segment 6) -1.7 cm (in segment 1) (Three episodes of hemorrhage occured, each two months apart.)	Discharge after follow-up
Case 6 (11)	44 year-old Female Breast cancer (Taking tamoksifen and transtuzumab)	2 arterial embolizations and 1 percutaneous drainage	Not specified	At the 7-month follow-up, the hematoma was found to have decreased in size
Case 7 (12)	60 year-old Male No comorbidities Pain onset after coughing	Visceral surgery (laparotomy)	17x14x5 cm	Discharge after follow-up
Case 8 (13)	43 year-oldu Female Steinert disease Nephrolithiasis (right)	Death occured following two days of right upper quadrant pain attributed no nephrolithiasis. The authopsy revealed approximately 2 liters of hemoperitoneum due to subcapsular hematoma of the liver. The cause of death was recorded as subcapsular hematoma of the liver.		

care. Among the reported cases, only one case (11.1%) resulted in death, and the cause of death was confirmed to be spontaneous subcapsular hepatic hemorrhage on autopsy (13). The remaining eight cases (88.8%) were discharged without adverse events.

Conclusion

Considering the clinical course of all previously reported cases, spontaneous subcapsular hemorrhage of the liver may resolve with mild symptoms within a few days. However, it also has the potential to rupture, which can lead to rapid hemodynamic deterioration and death. Conservative treatment and clinical follow-up are the first-line approaches for patients with stable hemodynamics after diagnosis. The patient's vital signs and blood parameters should be closely monitored, and the extent of bleeding should be tracked through radiological imaging. In cases of hemodynamic instability or rapidly expanding hemorrhage, percutaneous interventions, arterial embolization, and surgery may be considered.

Ethics

Informed Consent: Consent was obtained from the patient and their relatives.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S., İ.D., B.T., Concept: E.S., Design: E.S., B.T., Data Collection or Processing: E.S., Analysis or Interpretation: E.S., Literature Search: E.S., İ.D., Writing: E.S., İ.D., B.T.

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LETTER TO THE EDITOR

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Innovations, Ethical Issues, and Market Dynamics in Aesthetic Dermatology

Estetik Dermatolojide Yenilikler, Etik Sorunlar ve Pazar Dinamikleri

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Dear Editor,

Aesthetic dermatology has rapidly become a burgeoning field in recent years, driven by technological innovations and increasing patient demand. This growth is supported by the development of innovative treatments aimed at improving skin health and appearance. Botulinum toxin and dermal fillers have emerged as effective tools in reducing signs of aging (1,2). Laser treatments, stem cell and exosome therapies, and chemical peels play crucial roles in skin rejuvenation, scar treatment, pigmentation correction, and addressing hair issues (3,4). These procedures, being minimally invasive, appeal to a broad patient base and contribute to making aesthetic dermatology services more accessible.

The market share of the aesthetic dermatology sector has significantly increased in recent years. This rise is linked to both technological advancements and the growing demand for aesthetic procedures. The popularity of minimally invasive procedures, in particular, attracts a wider patient demographic. This trend enhances the accessibility of aesthetic dermatology services and contributes to market expansion. The global aesthetic market reached billions of dollars in the 2020s, with expectations for continued growth in the coming years. This growth is fueled by the development of new technologies and the increasing societal acceptance of aesthetic procedures.

However, the rapid advancements in this field also bring ethical and safety concerns. Notably, unauthorized "back-alley" practices pose serious health risks. Such procedures can lead to infections, allergic reactions, and permanent damage. The rise of these unauthorized practices endangers patient safety and tarnishes the reputation of the aesthetic dermatology field. Therefore, aesthetic dermatological procedures should only be performed by trained and certified specialists.

Moreover, it is crucial for practitioners outside the field to refrain from performing aesthetic dermatological procedures. Such practices can jeopardize patient safety and lead to undesirable complications. Aesthetic dermatology requires specialized knowledge and experience, and thus should only be conducted by professionals who have specialized in this area. When practitioners outside the field perform these procedures, it not only risks patient safety but also violates professional ethical standards.

Continuous education and certification processes for dermatology specialists working in aesthetic dermatology are critical for ensuring patient safety and enhancing the effectiveness of treatments. Educational programs facilitate the integration of new technologies and treatment methods, while certification processes ensure that practitioners meet specific standards. These processes also help prevent unauthorized practices.

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The future of aesthetic dermatology depends on balancing innovative treatments with ethical standards. Innovations in aesthetic dermatology focus on minimal invasive and regenerative approaches to achieve natural and healthy results. Innovative filler applications that enhance skin hydration and treatments supporting cellular regeneration are at the forefront. Technologies such as energy-based skin tightening and light therapy help boost collagen production, aiding skin rejuvenation. Additionally, artificial intelligence enables personalized treatments, while laser technologies improve the effectiveness of drug delivery beneath the skin. This balance will enhance patient satisfaction and uphold the field's integrity (5). More innovations and developments are expected in the future of aesthetic dermatology. Particularly, personalized treatment approaches and the integration of new technologies will improve the effectiveness and safety of procedures. Additionally, strengthening aesthetic dermatology will contribute to preventing unauthorized practices and ensuring patient safety.

The increasing acceptance of aesthetic dermatology procedures in society also influences cultural norms and perceptions of beauty. Media and social media platforms boost the popularity of aesthetic procedures and drive demand in this field. This trend facilitates the reach of aesthetic dermatology services to broader audiences while also impacting the evolution of beauty standards. However, the importance of ethical and responsible practices becomes even more critical in this process. Raising public awareness and providing accurate information are crucial for ensuring that aesthetic dermatology procedures are conducted safely and ethically.

The growth of the aesthetic dermatology sector also has significant economic impacts. Innovations in this field create new job opportunities and increase employment in the healthcare sector. Additionally, the widespread adoption of aesthetic procedures enhances individuals' self-confidence, positively affecting their social lives. However, for this growth to be sustainable, it is essential to maintain ethical standards and prioritize patient safety.

Conclusion

In conclusion, aesthetic dermatology holds great potential both scientifically and commercially. However, realizing this potential fully requires the meticulous application of ethical and safety standards. This approach will enhance patient satisfaction and ensure the long-term success of the aesthetic dermatology field. This guidance can contribute to future studies by providing direction.

Keywords: Aesthetic dermatology, ethics, marketing

Anahtar kelimeler: Estetik dermatoloji, etik, pazarlama

Ethics

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2024 REFEREE INDEX