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Kıymetli okuyucular;
Hitit Medical Journal dergimizin yeni sayısı ile karşınızdayız.
Dergimiz her geçen gün bilim dünyasının ilgisini daha fazla çekmektedir. Ulusal indekslerin yanında uluslararası indekslerde de taranmaya başlayarak tüm dünyaya açılmıştır. Bu durum ekibimizi hem heyecanlandırmış hem de gelecekteki çalışmalarımız için ciddi motivasyon artışına yol açmıştır. Yoğun ilgiye karşılık verebilmek adına makale değerlendirme süreçlerini en kısa sürede tamamlamak ve kabul edilmiş makaleleri dergimiz sayılarında mümkün olduğu kadar en kısa sürede yayımlamak için büyük çaba sarf ediyoruz. Akademik dünyaya katkıda bulunmak için hazırladıkları makaleleri dergimiz aracılığı ile bilim dünyasına sunmayı tercih eden tüm yazarlar ve bu makalelere ilgi gösteren tüm okuyucularımıza sonsuz teşekkürlerimizi iletiyoruz.
Bu sayıda 11 adet orijinal/araştırma olmak üzere farklı alanlarda toplam 14 makaleyi bilim dünyasına sunuyoruz.
Tüm okuyucularımıza keyifli ve yararlı okumalar diliyoruz.
Saygılar...

Doç. Dr. Abdulkerim YILDIZ
HMJ Editöryal Kurul adına

From the Editor

Dear readers;
We are here with the new issue of our Hitit Medical Journal.
Our journal attracts more and more attention from the scientific world every day. It has started to be indexed in international indexes as well as national indexes and has opened up to the whole world. This situation both excited our team and led to a serious increase in motivation for our future work. In order to respond to the intense interest, we make great efforts to complete the article evaluation processes and to publish accepted articles in the issues as soon as possible. We would like to express our endless gratitude to all authors who choose to present the articles they have prepared to contribute to the academic world to the scientific world through our journal, and to all our readers who show interest in these articles.
In the current issue, we present a total of 14 articles in different fields, 11 of which are original/research paper.
We wish all our readers enjoyable and useful reading.
With our respects...

Doç. Dr. Abdulkerim YILDIZ
On behalf of the HMJ Editorial Board

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The Effects of Religious Belief Level and Psychological Resilience on the Severity of Fibromyalgia Symptoms

Dini İnanç Düzeyi ve Psikolojik Dayanıklılığın Fibromiyalji Belirtilerinin Şiddeti Üzerindeki Etkileri

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The Effects of Religious Belief Level and Psychological Resilience on the Severity of Fibromyalgia Symptoms

Abstract

Objective: The effects of religiousness, forgiveness, and psychological resilience in patients with fibromyalgia have been investigated with regard to various aspects in the literature. However, there is no study investigating the effects of these concepts collectively in patients with fibromyalgia symptoms.The aim of this study was to investigate whether religious belief, forgiving nature and psychological resilience had any relationship with fibromyalgia symptom burden.

Material and Method: This descriptive study included 49 patients aged between 18–65 years with a diagnosis of fibromyalgia syndrome (FMS) who had applied to the out-patient clinic of the Physical Therapy and Rehabilitation Department of a University Hospital between 15 December 2019 and 15 April 2020.

Results: There were a total of 49 female patients in this study. The mean age of the patients participating in the study was 45.04 ± 9.25 years. Religiousness was found to be significantly associated with some subscales of psychological resilience. Additionally, most subscales of psychological resilience were significantly related with the severity of fibromyalgia. The level of religious belief influenced the relationship between psychological resilience and the severity of fibromyalgia.

Conclusion: In this study, it has been found that religious belief and forgiveness levels did not have a direct effect on fibromyalgia symptoms. Most of the subscales of psychological resilience were found to be associated with the severity of fibromyalgia symptoms. It is clear that psychological resilience has an effect on the severity of fibromyalgia symptoms, but further research is needed to assess mechanisms

Keywords: Fatigue, fibromyalgia, forgiveness, psychological resilience, religious belief.

Özet

Amaç: Literatürde fibromiyaljili hastalarda dindarlık, bağışlayıcılık ve psikolojik dayanıklılığın etkileri çeşitli açılardan araştırılmıştır. Ancak fibromiyalji semptomları olan hastalarda bu kavramların etkilerini toplu olarak araştıran bir çalışma bulunmamaktadır. Bu çalışmanın amacı, dini inanç, bağışlayıcılık ve psikolojik dayanıklılığın fibromiyalji semptom yükü ile ilişkisi olup olmadığını araştırmaktır.

Gereç ve Yöntem: Tanımlayıcı tipte olan bu çalışmaya, 15 Aralık 2019 ile 15 Nisan 2020 tarihleri arasında bir Üniversite Hastanesi Fizik Tedavi ve Rehabilitasyon Bölümü polikliniğine başvuran fibromiyalji sendromu (FMS) tanısı ile başvuran yaşları 18-65 arasında değişen 49 hasta dahil edildi.

Bulgular: Bu çalışmada toplam 49 kadın hasta vardı. Katılımcıların yaş ortalaması 45,04 ± 9,25 yıl idi. Dindarlık, psikolojik dayanıklılığın bazı alt boyutlarıyla anlamlı olarak ilişkili bulundu. Ek olarak, psikolojik dayanıklılığın çoğu alt ölçeği, fibromiyaljinin şiddeti ile önemli ölçüde ilişkiliydi. Dini inanç düzeyi, psikolojik dayanıklılık ile fibromiyaljinin şiddeti arasındaki ilişkiyi etkilemiştir.

Sonuç: Bu çalışmada dini inanç ve bağışlama düzeylerinin fibromiyalji semptomları üzerinde doğrudan etkisinin olmadığı bulunmuştur. Psikolojik dayanıklılığın alt ölçeklerinin çoğunun fibromiyalji semptomlarının şiddeti ile ilişkili olduğu bulundu. Psikolojik dayanıklılığın fibromiyalji semptomlarının şiddeti üzerinde bir etkisi olduğu açıktır, ancak mekanizmaları değerlendirmek için ileri araştırmalara ihtiyaç vardır.

Anahtar Sözcükler: Bağışlama, dini inanç, fibromiyalji, psikolojik dayanıklılık, yorgunluk.

Introduction

Fibromyalgia is a systemic disorder characterized by diffuse pain in various parts of the body and fatigue, sleep disorders, headache, and sometimes, cognitive disorders (1). Around 2–8% of the population suffers from this disease and there are pharmacological and non-pharmacological options supported by high-quality evidence for its treatment (2). One of the two main 'pathways' that allegedly reduce the severity of fibromyalgia symptoms is the psychological pathway (based on psychological resilience), while the other is the physical pathway in relation to physical activity levels (3).

Psychological resilience is defined as mental processes and behaviors that are effective in protecting an individual from potential negative effects of stress factors (4). The effects of psychological resilience on disease severity in patients with fibromyalgia and chronic pain disorder and factors related to psychological resilience have been widely investigated and different findings on this subject are available in the literature. Significant differences have been observed in patients with chronic pain disorder that were defined to have high or low psychological resilience, in terms of their ways of coping with their disease, their attitudes and beliefs related to pain, their tendency to be crippled by the condition, their positive and negative social responses to pain, and health characteristics and compliance with treatment (5). It has been found that patients who can adapt to higher levels of pain and are less affected by fibromyalgia syndrome (FMS) have fewer depressive symptoms, pain disaster, and psychological inflexibility and these factors are also considered to be among the sources of psychological resilience in FMS (6).

In the social field, religiousness has been explained by Coştu as a way of thinking, feeling and behavior towards religious beliefs and practices. Normative-style religious orientation is defined as the basic determinative, actual and moral teachings of the religion that determine the way of religious life of the individual (7). Many studies have shown that there is a direct relationship between religious belief and health outcomes, including mortality, physical illness, mental illness, quality of life and coping with illness (8, 9).

It has been reported that forgiveness (having a forgiving nature) is among the resilience factors that affect health characteristics; furthermore, forgiveness may be useful in minimizing stress-related disorders (10). A positive relationship was found between forgiveness and physical health (11). A high level of forgiveness in patients with FMS, both towards themselves and others, has been demonstrated to be beneficial for the patient's mental health, quality of life and anger level (12). It has been claimed that forgiveness has a direct positive effect on recovery in patients with FMS and chronic fatigue syndrome, by reducing anger, stress and other negative sensations (13).

The effects of religiousness, forgiveness, and psychological resilience in patients with fibromyalgia have been investigated with regard to various aspects in the literature. However, there is no study investigating the effects of these concepts collectively in patients with fibromyalgia symptoms. For this purpose, we investigated the relationships between religious belief and forgiveness levels, psychological resilience and symptom severity in a group of women with fibromyalgia.

Material and Method

This descriptive study included 49 patients aged between 18–65 years with a diagnosis of FMS who had applied (for routine follow-up) to the outpatient clinic of the Physical Therapy and Rehabilitation Department of Hitit University Corum Erol Olcok Training and Research Hospital between 15 December 2019 and 15 April 2020. Among eligible patients, all participants meeting inclusion/exclusion criteria provided written informed consent for the use of data in scientific research. The study conformed with the Helsinki Declaration (including 2013 amendments). The study was granted approval by the local ethics committee (Date:11.12.2019, No:110). Attending physicians

applied the measurement scales used in this study.

Inclusion criteria

The inclusion criteria of the study were accepted as being between the ages of 18-65 years, being a woman, having a diagnosis of fibromyalgia, accepting to participate in the study of their own accord, and not having any mental illness that would limit reasoning when completing questionnaires (such as mental retardation or psychotic disorder). All individuals included in the study were Muslims (followers of the Islam religion). Only female patients were included because almost all of the patients admitted to the Department of Physical Therapy and Rehabilitation with a diagnosis of fibromyalgia were women. Three patients refused to participate in the study because they found the questions about their religious beliefs disturbing, and one patient did not have time.

Exclusion criteria

Illiterate patients or those with insufficient cognitive ability (mental retardation, dementia, etc.) to read or understand and complete the scales, and those with any limiting condition that could prevent them from understanding the acceptance of participation with their own free will, were excluded.

Sample size estimations and power analysis

Sample size calculation was based on correlation analysis used to test the primary hypothesis. It was found that a minimum of 46 individuals needed to be included to be able to assess significant relationships in the groups, using $\alpha = 0.05$ error (95% confidence interval), and 80% power ($1-\beta=0.80$). When needed, post-hoc power analysis was performed to assess power for statistically significant primary hypotheses, with respect to $\alpha = 0.05$ error. The G*power (version 3.1.9.6) package was used for a priori (sample size estimation) and post-hoc analyses. Patients were consecutively included in the study until the sample size was reached. When the post-hoc power analysis was calculated, it was seen that the power was higher than 80% in all analyses.

Fibromyalgia diagnostic criteria

All FMS diagnoses were based on the diagnostic criteria of the American College of Rheumatology (ACR) (2016) (14).

1. Widespread pain index (WPI): Number of painful body regions in the last week (score range 0–19). Shoulder girdle, left-right; hip, left-right; chin, left-right; back; upper arm, left-right; thigh, left-right; chest and waist; forearm, left-right; leg, left-right; abdomen and neck.
2. Symptom severity scale

- Fatigue
- Getting up tired in the morning
- Presence of cognitive symptoms
- Presence of general somatic symptoms

Data collection

Patient-related sociodemographic characteristics (name, age, educational and marital status, and occupation) and disease-related clinical information were obtained. Functional status was assessed using the Fibromyalgia Impact Questionnaire (FIQ). The level of religious belief was measured with the Religious Orientation Scale, forgiveness with the Tendency to Forgiveness Scale, and resilience with the Psychological Resilience Scale for adults.

Fibromyalgia Impact Questionnaire (FIQ)

The original form of the scale has been developed by Burckhardt CS and colleagues (15). This scale measures physical function, well-being, missing work, difficulty in performing professional duties at the workplace, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. Except for “the ability to feel good” parameter, lower scores are indicative of lower disease impact (better). The FIQ was filled by the patients themselves. Each subsection is scored to a maximum of 10 points; thus, the maximum total score is 100. Of note, average FMS patients score around 50 points, while severe cases score >70 points (15, 16).

Psychological resilience scale for adults

This is a 5-point Likert-type scale tool consisting of 33 questions and developed by Friborg O and colleagues

(17). Scores range from 33 to 165 points. While some assess scores with minor variations, traditionally, the answer boxes are evaluated as 1-2-3-4-5 points from left to right, while reverse-scored questions (numbered 1, 3, 4, 8, 11, 12, 13, 14, 15, 16, 23, 24, 25, 27, 31 and 33) are scored from right to left (17, 18).

Religious orientation scale

This scale was developed by Coştu Y (7). It consists of 37 items and is in a 5-point Likert scale format. Normative-style religious orientation is defined as the basic determinative, actual, and moral teachings of the religion that determine the way of religious life of the individual. There are 30 items in total, 6 of which are scored inversely and 24 of which are scored normally in the subscale of normative-style religious orientation. There are 7 items in the 'popular-style religious orientation' subscale. Popular-style religious orientation has been defined as the composition of rituals of traditional religious/mystical styles of the population (7). We used only the normative-style religious orientation subscale in our study.

Tendency to forgiveness scale

This scale was developed by Ayten A (19). It is comprised of 20 items (Likert-type), all responses are based on the patients' interpretation of the self-appropriateness of each item (19). Scores closer to 5 points indicate higher levels of forgiveness, and lower scores indicate lower levels of forgiveness.

Statistical Analysis

Statistical analysis of the data collected in our study was performed with the SPSS (Version 22, Chicago, IL, USA) package program. Descriptive statistics of continuous variables obtained by measurements were reported using mean ± standard deviation or median (min-max) depending on their normality of distribution. Nominal or ordinal variables were described with absolute and relative frequency. The detection of distribution was performed by the Shapiro-Wilk test. The correlations between religious beliefs, level of forgiveness, psychological resilience scale scores and the severity of fibromyalgia symptoms obtained from the responses of the patients were analyzed by the calculation of Spearman correlation coefficient for each pair. Univariate regression analysis was used to model the relationships between religious attitude and structural style and between religious attitude and social resources variables that demonstrated significant differences. All analyses were subject to a significance threshold of <0.05 (*p value*).

Results

All individuals included in the study were Muslims. Only female patients were included because almost all of the patients admitted to the Department of Physical Therapy and Rehabilitation with a diagnosis of fibromyalgia were women. Three patients refused to participate in the study because they found the questions about their religious beliefs disturbing, and one patient did not have time.

Table I. Sociodemographic characteristics of patients

	Groups	Frequency	Percent (%)
Occupation	Housewife	39	79.6
	Worker	7	14.3
	Officer	2	4.1
	Retired	1	2.0
Education	Primary school	33	67.3
	Elementary school	7	14.3
	High school	6	12.2
	University	3	6.1
Marital status	Married	45	91.8
	Divorced	4	8.2
Number of children	0	1	2.0
	1	2	4.1
	2	22	44.9
	3	20	40.8
	4	2	4.1
	5	2	4.1
	Total	49	100

There were a total of 49 female patients in this study. Participants' mean age was 45.04 ± 9.25

(min-max: 28–65) years. Other sociodemographic characteristics are depicted in Table 1. Descriptive statistics of religious attitude, forgiveness, and psychological resilience subscale scores and WPI, symptom severity scale, total score and FIQ values are presented in Table 2. No statistically significant correlation was found between religious attitude or forgiveness scale scores and WPI, symptom severity scale, total score, and FIQ values (*p>0.05;* Table 3).

Table II. Descriptive statistics of the scale scores (n=49)

	Mean ± SD	Median (min-max)
Widespread Pain Index	13.14 ± 2.49	13 (7-18)
Symptom Severity Scale	8.86 ± 1.63	9 (5-12)
Total Score	22.00 ± 3.35	22 (14-29)
FIQ	68.11 ± 16.42	69.6 (21.6-94.3)
Forgiveness	65.35 ± 8.95	67 (44-80)
Religious Attitude	130.76 ± 14.71	131 (92-150)
Structural Style	14.22 ± 3.96	14 (4-20)
Future Perception	11.98 ± 5.02	12 (4-20)
Family Cohesion	22.08 ± 5.82	23 (6-30)
Self-Perception	21.02 ± 5.55	22 (9-30)
Social Competence	21.27 ± 5.60	22 (6-30)
Social Resources	26.67 ± 6.00	27 (11-35)

Statistically significant weak positive correlations were found between religious attitude and the 'structural style' and 'social resources' subsection scores of the psychological resilience scale (*r=0.392, p=0.005; r=0.413, p=0.003*, respectively). No significant relationship was found between religious attitude and other psychological resilience subscale scores (*p>0.05*). No statistically significant correlation was found between forgiveness scale scores and psychological resilience subscale scores (structural style, future perception, family cohesion, self-perception, social competence, and social resources) (*p>0.05*) (Table 4).

Table III. Spearman correlation coefficients between religious attitude and forgiveness scale scores and widespread pain index (WPI), symptom severity scale (SSS), total score and FIQ values (n=49)

		WPI	SSS	Total Score	FIQ
Religious Attitude	*r*	0.005	-0.005	-0.006	-0.231
	p	0.971	0.975	0.968	0.111
Forgiveness	*r*	0.153	-0.083	0.103	-0.028
	p	0.295	0.569	0.480	0.846

Statistically significant negative correlations were found between structural style scores and FIQ values, between future perception scores and symptom severity scale, total score and FIQ values, between self-perception scores and symptom severity scale, total score and FIQ values, between social competence scores and total score and FIQ values, and between social resource scores and FIQ values (Table 5).

As a result of univariate regression analysis, we found that lower religious attitude is associated with and structural style (OR: 0.086, 95%CI: 0.024 - 0.161, *p=0.024*) and social resources (OR: 0.140, 95%CI: 0.027 - 0.252, *p=0.016*).

Table IV. Spearman correlation coefficients between religious attitude and forgiveness scale scores and psychological resilience subscale scores (structural style, future perception, family cohesion, self-perception, social competence and social resources) (n=49)

		Structural Style	Future Perception	Family Cohesion	Self-Perception	Social Competence	Social Resources
Religious Attitude	*r*	**0.392****	0.244	0.121	0.096	0.203	**0.413****
	p	**0.005**	0.091	0.409	0.511	0.161	**0.003**
Forgiveness	*r*	-0.017	0.255	0.237	0.224	0.104	0.248
	p	0.906	0.077	0.101	0.122	0.477	0.085

Table V. Spearman correlation coefficients between psychological resilience subscale scores (structural style, future perception, family cohesion, self-perception, social competence and social resources) and widespread pain index (WPI), symptom severity scale (SSS), total score and FIQ values before and after checking religious attitude and forgiveness scale scores

Control Variables			WPI	SSS	Total Score	FIQ
No	Structural Style	*r*	-0.127	-0.128	-0.188	**-0.392**
		p	0.385	0.381	0.195	**0.005****
	Future Perception	*r*	-0.220	**-0.313**	**-0.313**	**-0.400**
		p	0.130	**0.028***	**0.029***	**0.004****
	Family Cohesion	*r*	-0.066	-0.195	-0.166	-0.210
		p	0.654	0.180	0.254	0.147
	Self-Perception	*r*	-0.209	**-0.339**	**-0.333**	**-0.354**
		p	0.149	**0.017***	**0.019***	**0.013***
	Social Competence	*r*	-0.231	-0.221	**-0.328**	**-0.408**
		p	0.111	0.127	**0.021***	**0.004****
	Social Resources	*r*	-0.063	-0.136	-0.156	**-0.344**
		p	0.668	0.352	0.283	**0.015***
Religious Attitude	Structural Style	*r*	-0.104	-0.226	-0.187	**-0.324**
		p	0.484	0.123	0.203	**0.024***
	Future Perception	*r*	-0.177	**-0.309**	-0.282	**-0.363**
		p	0.228	**0.033***	0.052	**0.011***
	Family Cohesion	*r*	-0.071	-0.206	-0.153	-0.268
		p	0.632	0.159	0.299	0.066
	Self-Perception	*r*	-0.217	**-0.326**	**-0.320**	**-0.300**
		p	0.139	**0.024***	**0.027***	**0.038***
	Social Competence	*r*	-0.215	-0.269	**-0.291**	**-0.329**
		p	0.143	0.064	**0.045***	**0.022***
	Social Resources	*r*	-0.002	-0.111	-0.055	-0.208
		p	0.991	0.453	0.709	0.156
Forgiveness	Structural Style	*r*	-0.111	-0.222	-0.191	**-0.357**
		p	0.451	0.129	0.195	**0.013***
	Future Perception	*r*	-0.217	**-0.297**	**-0.305**	**-0.395**
		p	0.138	**0.040***	**0.035***	**0.005****
	Family Cohesion	*r*	-0.103	-0.198	-0.172	-0.274
		p	0.488	0.177	0.242	0.060
	Self-Perception	*r*	-0.254	**-0.320**	**-0.344**	**-0.315**
		p	0.082	**0.026***	**0.017***	**0.029***
	Social Competence	*r*	-0.227	-0.262	**-0.295**	**-0.358**
		p	0.121	0.072	**0.042***	**0.013***
	Social Resources	*r*	-0.041	-0.102	-0.080	-0.251
		p	0.782	0.492	0.590	0.085

Discussion

No statistically significant relationship was found between religious belief level and fibromyalgia symptom burden. In a review article on the effect of religiosity and spirituality levels on various pain-related conditions in patients with chronic pain, it has been reported that there was no statistically significant relationship between religiosity and severity of pain in most studies, but religiosity has significant relationships with some factors that also affect pain (20). There is no evidence of the direct effects of religiosity on the severity of fibromyalgia symptoms, although the indirect effects of religiosity have been reported in patients with chronic pain disorders (associated with well-being and positive coping mechanisms), while religiosity has also been reported to influence the diurnal secretion of cortisol in fibromyalgia, and it has been suggested to relieve the physiological effects of stress (21, 22).

Similarly, rather than establishment of direct effects of forgiveness on symptom severity, various studies investigating the relationships between forgiveness and fibromyalgia have reported beneficial effects on quality of life, well-being, emotions, catastrophizing and coping behavior in patients with fibromyalgia symptoms (11-13, 23). In line with all these findings, we have also not found any direct influence of religious belief and forgiveness on the severity of fibromyalgia symptoms.

In the present study, we determined mild-moderate relationships between the level of religious belief and the 'structural style' and 'social resources' subscales of the psychological resilience scale. It has been reported that the structural style score of this scale evaluates the subject's ability to support, plan and organize daily routines (17). In the literature, no study was found to explain the relationship between these abilities and religious beliefs. However, we thought there might be a way to explain, or better, to quantify these relationships. We thought that worship-related practices, such as ablution and prayer, which are performed at certain times of the

day in the Islamic religion, may help the individual improve their planning and organizing skills. Although the correlation coefficient was low, the significant relationship between religious belief and the structural style subscale may support this suggestion. It has been reported that the social resources subscale assesses the individual's access to external support from their friends and relatives, and the individual's ability to provide support to those surrounding them (17). The beneficial effect of religious beliefs on a person's ability to cope with diseases has previously been associated with the humanitarian and divine support that helps to reduce isolation and loneliness (24). We thought that this feature of religiousness could have been exemplified by the correlation between social support and religiousness that was determined with our results, although it must be noted that this correlation was also rather weak.

There was no statistically significant correlation between forgiveness scale scores and psychological resilience subscale scores. It has been reported that forgiveness contributes to coping mechanisms by reducing the negative effects of intense stress (10). However, although the concepts of coping and resilience are often used interchangeably, there is evidence that they are conceptually completely different concepts. While psychological resilience is described as a concept that affects how an adverse event is evaluated, coping is described as a concept that explains the actual response to stress exposure due to such events (4). In previous studies, forgiveness has been shown to be useful in areas related to coping mechanism in fibromyalgia, such as mental health, quality of life, reducing anger, stress and other negative sensations (12, 13). However, we did not investigate the effect of forgiveness on coping styles in this study. We concluded that some personality traits and mental schemes, which we did not investigate in this study, may be effective on psychological resilience levels rather than forgiveness levels.

We have found that the structural style and social resources subscales of the psychological resilience scale were associated with functionality scale, while future perception, self-perception and social competence subscales were associated with both symptom severity and functionality. It has been claimed that psychological resilience plays a role in the stress response system, affects the degree of susceptibility to chronic stress; thus, resilience may be a concept that can be a therapeutic target in chronic pain disorders (25). In a study comparing two groups with high and low psychological resilience among patients with chronic pain disorder, there were significant differences between the groups in terms of their coping styles, pain orientations and beliefs, tendency to catastrophizing, positive and negative social responses to pain, attention to their health, and adherence to drug treatments (5). Furthermore, psychological resilience has been shown to be associated with symptom burden in patients with fibromyalgia (26). In a study investigating the protective role of psychological resilience in breast cancer patients with FMS, it was reported that psychological resilience was associated with pain, fatigue and functional capacity (27). Similarly, we have found a significant relationship between the scores of all subscales of the psychological resilience scale (except for the family cohesion subscale) and the scores of the scales that reflect symptom severity or level of functionality in patients with fibromyalgia.

After checking the scores of religious belief and forgiveness scales with partial correlation analysis, correlations between psychological resilience and symptom burden were determined. When the effect of religious belief level on psychological resilience was eliminated by that statistical method, it was found that the significant relationships between future perceptions subscale and the total fibromyalgia symptom level and the significant relationships between social resources subscale and the level of functionality in patients with fibromyalgia had disappeared. When the effect of the forgiveness scale on psychological resilience was eliminated, it was found that the significant relationship between

the social resources subscale and the level of functionality in patients with fibromyalgia had disappeared. In a review article assessing whether religiousness and spirituality were influential on mental health, these attributes were regarded as the leading reasons for preferring religious coping ways in psychiatric and physical diseases due to the fact that religious belief provides some sense of meaning and purpose in difficult living conditions; thereby enabling the assertion of an optimistic and hopeful worldview that reduces the need for personal control over events; thus, increasing mental support and reducing loneliness (24). The current study was partially based on this claim and we hypothesized that religious belief could reduce the severity of fibromyalgia symptoms by positively affecting future perception –as it was suggested that religious belief gives a sense of meaning and purpose in difficult living conditions, provides an optimistic and hopeful worldview and reduces the need for personal control over events. Our take on this topic was that, the fundamental Islamic belief of "destiny is in the hands of Allah (the omnipotent god of Islam)" would represent this function. We concluded that religious beliefs providing support to reduce loneliness can positively affect the social resources subscale, thereby increasing the functionality of patients with fibromyalgia. It is also notable that worship-related practices with socializing effects such as performing Salaat (Islamic prayer which is performed 5 times a day) as a community in mosques may also cause a positive effect in this regard.

Our results indicate that forgiveness has no effect on psychological resilience. However, when the effect of forgiveness was eliminated statistically, it was found that the significance of the social resources subscale's impact on functionality in fibromyalgia had disappeared, suggesting that forgiveness has an effect, albeit very limited. It has been claimed that forgiveness contributes to psychological well-being by providing less negative affect and more positive relationships (28). We thought that forgiveness's positive relationships might explain the impact it had on the social resources subscale. We thought that the resultant positive effects of forgiveness could explain the influence on the social resources subsection. We interpreted this relationship to the positivity provided by forgiveness on relationships, which possibly helped the person to have increased social support, thereby causing a positive influence on function in fibromyalgia.

We think that the most important limitation of our study may be associated with the possibility that individuals were not comfortable in responding accurately to the various scales employed, especially the religious attitude scale. This was because, in our country, people may not want to objectively answer questions related to religious belief due to a fear of stigmatization. Although they were told that their information would not be shared and the results would be de-identified prior to use in this research, we believe that subjects may have had a tendency to provide answers that would be more acceptable in our country. The second limitation is the limited sample size. The results of studies to be conducted with the participation of more fibromyalgia patients and in different populations may differ from our study.

Conclusion

In this study, it has been found that religious belief and forgiveness levels did not have a direct effect on fibromyalgia symptoms. Most of the subscales of psychological resilience were found to be associated with the severity of fibromyalgia symptoms. While religious belief strengthened the relationship between psychological resilience subscales and fibromyalgia symptom burden, forgiveness was observed to have a very weak effect on these relationships. We think that our study once again draws attention to the concept of psychological resilience in fibromyalgia patients and will be a resource for further research in which the factors affecting this concept will be investigated. In future studies, with the participation

of more people, examining the effects of living in different religions and different populations on the symptoms of fibromyalgia may reinforce the results of our study.

References

1. Neumeister MW, Neumeister EL. Fibromyalgia. Clin Plast Surg 2020;47:203-213.
2. Clauw DJ. Fibromyalgia: a clinical review. JAMA 2014;311:1547-1555.
3. Pulido-Martos M, Luque-Reca O, Segura-Jiménez V, et al. Physical and psychological paths toward less severe fibromyalgia: A structural equation model. Ann Phys Rehabil Med 2020;63:46-52.
4. Fletcher D, Sarkar M. Psychological resilience. Eur Psychol 2013;18:12-23.
5. Karoly P, Ruehlman LS. Psychological "resilience" and its correlates in chronic pain: findings from a national community sample. Pain 2006;123:90-97.
6. Angarita-Osorio N, Pérez-Aranda A, Feliu-Soler A, et al. Patients With Fibromyalgia Reporting Severe Pain but Low Impact of the Syndrome: Clinical and Pain-Related Cognitive Features. Pain Pract 2020;20:255-261.
7. Coştu Y. Dine Normatif ve Popüler Yaklaşım:"Bir Dini Yönelim Ölçeği Denemesi. Hitit Üniversitesi İlahiyat Fakültesi Dergisi 2009;8:119-139.
8. Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality, and medicine: implications for clinical practice. Mayo Clin Proc 2001;76:1225-1235.
9. Koenig HG. Religion and medicine II: religion, mental health, and related behaviors. Int J Psychiatry Med 2001;31:97-109.
10. Toussaint L, Shields GS, Dorn G, Slavich GM. Effects of lifetime stress exposure on mental and physical health in young adulthood: How stress degrades and forgiveness protects health. J Health Psychol 2016;21:1004-1014.
11. Lee YR, Enright RD. A meta-analysis of the association between forgiveness of others and physical health. Psychol Health 2019;34:626-643.
12. Offenbaecher M, Dezutter J, Kohls N, et al. Struggling with adversities of life: The role of forgiveness in patients suffering from fibromyalgia. Clin J Pain 2017;33:528-534.
13. Toussaint L, Overvold-Ronningen M, Vincent A, et al. Implications of forgiveness enhancement in patients with fibromyalgia and chronic fatigue syndrome. J Health Care Chaplain 2010;16:123-139.
14. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319-329.
15. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728-733.
16. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int 2000;20:9-12.
17. Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M. A new rating scale for adult resilience: what are the central protective resources behind healthy adjustment? Int J Methods Psychiatr Res 2003;12:65-76.
18. Basim HN, Cetin F. The reliability and validity of the Resilience Scale for Adults-Turkish Version. Turk Psikiyatri Derg 2011;22:104.
19. Ayten A. Affedicilik ve Din: Affetme Eğilimi ve Dindarlıkla İli § kisi Üzerine Ampirik Bir Ara § tırma. Marmara Üniversitesi İlahiyat Fakültesi Dergisi 2009:111-128.
20. Ferreira-Valente A, Sharma S, Torres S, et al. Does Religiosity/Spirituality Play a Role in Function, Pain-Related Beliefs, and Coping in Patients with Chronic Pain? A Systematic Review. J Relig Health 2019. Online ahead of print.
21. Baetz M, Bowen R. Chronic pain and fatigue: Associations with religion and spirituality. Pain Res Manag 2008;13:383-388.
22. Dedert EA, Studts JL, Weissbecker I, Salmon PG, Banis PL, Sephton SE. Religiosity may help preserve the cortisol rhythm in women with stress-related illness. Int J Psychiatry Med 2004;34:61-77.
23. Vallejo MA, Vallejo-Slocker L, Rivera J, Offenbächer

M, Dezutter J, Toussaint L. Self-forgiveness in fibromyalgia patients and its relationship with acceptance, catastrophising and coping. Clin Exp Rheumatol 2020;38 Suppl 123:79-85.
24. Koenig HG. Research on religion, spirituality, and mental health: a review. Can J Psychiatry 2009;54:283-291.
25. Casale R, Sarzi-Puttini P, Botto R, et al. Fibromyalgia and the concept of resilience. Clin Exp Rheumatol 2019;37 Suppl 116:105-113.
26. Mcallister SJ, Vincent A, Hassett AL, et al. Psychological Resilience, Affective Mechanisms and Symptom Burden in a Tertiary-care Sample of Patients with Fibromyalgia. Stress Health 2015;31:299-305.
27. Schrier M, Amital D, Arnson Y, et al. Association of fibromyalgia characteristics in patients with non-metastatic breast cancer and the protective role of resilience. Rheumatol Int 2012;32:3017-3023.
28. Hill PL, Allemand M. Forgivingness and adult patterns of individual differences in environmental mastery and personal growth. J Res Pers 2010;44:245-250.

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Fetal Femoral Artery Doppler Evaluation in Late-Onset Fetal Growth Restriction: A Case-Control Study

Geç Başlangıçlı Fetal Büyüme Geriliğinde Fetal Femoral Arter Doppler Değerlendirmesi: Vaka Kontrol Çalışması

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Fetal Femoral Artery Doppler Evaluation in Late-Onset Fetal Growth Restriction: A Case-Control Study

Abstract

Objective: To compare the femoral artery and other ultrasonographic Doppler measurements between fetuses with late-onset fetal growth restriction and uncomplicated fetuses.

Material and Method: This prospective cohort study was conducted with 168 patients, including 83 pregnancies presenting with late-onset fetal growth restriction and 85 uncomplicated control pregnancies at similar gestational weeks. The study group was further divided into two according to the neonatal intensive care unit requirements. Demographic characteristics, obstetric characteristics, femoral artery and other ultrasonographic Doppler measurements, and pregnancy outcomes were compared between the groups.

Results: Uterine artery pulsatility index, umbilical artery systolic/diastolic ratio, and peak systolic velocity of the middle cerebral artery were similar between the study and control groups. However, while the middle cerebral artery pulsatility index was significantly lower in the study group, the femoral artery pulsatility index value was significantly higher ($p<0.001$ and $p=0.002$, respectively). When the two subgroups of the study group were compared according to the neonatal intensive care unit requirements, their femoral artery and other Doppler measurements were similar. Estimated fetal weight was statistically lower in the group requiring neonatal intensive care unit ($p=0.033$).

Conclusion: The femoral artery pulsatility index measurement was higher in the late-onset fetal growth restriction cases than in the healthy controls. The Doppler examination of the femoral artery was not found to be effective in demonstrating adverse perinatal outcomes.

Keywords: Adverse perinatal outcomes, cerebroplacental ratio, femoral artery doppler, fetal growth restriction.

Özet

Amaç: Femoral arter ve diğer ultrasonografik Doppler ölçümlerini geç başlangıçlı fetal büyüme geriliği olan fetüsler ile komplike olmayan fetüsler arasında karşılaştırmak.

Gereç ve Yöntem: Bu prospektif kohort çalışması geç başlangıçlı fetal gelişme geriliği saptanan 83 çalışma grubu gebe ile benzer gebelik haftasına sahip 85 komplike olmayan kontrol grubu gebe dahil olmak üzere 168 hasta ile gerçekleştirilmiştir. Aynı zamanda yenidoğan yoğun bakım ünitesi gereksinimine göre çalışma grubu ikiye ayrıldı. Gruplar arasında demografik özellikler, obstetrik özellikler, femoral arter ve diğer ultrasonografik doppler ölçümleri ve gebelik sonuçları karşılaştırıldı.

Bulgular: Uterin arter pulsatilite indeksi, umbilikal arter sistolik/diyastolik oranı ve orta serebral arterin pik sistolik hızı çalışma ve kontrol grupları arasında benzerdi. Ancak çalışma grubunda orta serebral arter pulsatilite indeksi anlamlı olarak düşük bulunurken, femoral arter pulsatilite indeksi anlamlı olarak yüksekti (sırasıyla, $p<0.001$ ve $p=0.002$). Çalışma grubunda yenidoğan yoğun bakım ünitesi gereksinimine göre iki grup karşılaştırıldığında femoral arter ve diğer doppler ölçümleri benzer izlendi. Tahmini fetal ağırlık, yenidoğan yoğun bakım ünitesi gerektiren grupta istatistiksel olarak daha düşüktü ($p=0.033$).

Sonuç: Geç başlangıçlı fetal büyüme geriliği olgularında femoral arter pulsatilite indeksi sağlıklı kontrollere göre daha yüksekti. Femoral arterin Doppler incelemesinin olumsuz perinatal sonuçları göstermede etkili olmadığı bulundu.

Anahtar Sözcükler: Femoral arter doppler, fetal büyüme geriliği, olumsuz perinatal sonuçlar, serebroplasental oran.

Introduction

Although fetal growth restriction (FGR) is difficult to define, it is basically a pathological growth restriction associated mainly with placental insufficiency (1). For the diagnosis of FGR, estimated fetal weight (EFW) or abdominal circumference (AC) determined by ultrasonography should be less than the 10th percentile for gestational age (2). FGR is associated with an increased risk of perinatal mortality and morbidity, and its incidence has been reported to reach 5.5% in some population-based studies (3). Depending on the gestational age at diagnosis, a broad classification of FGR into early-onset (<32 weeks) and late-onset (≥32 weeks) categories has been proposed. The rationale for this classification is based on the differences in severity, natural disease course, doppler findings, placental findings, and treatments between these two FGR phenotypes (4). Late-onset FGR (LO-FGR) is difficult to detect and is often overlooked. In this phenotype, fetal dimensions may be within normal ranges, and measurable Doppler changes are less prominent (5).

The presence of placental insufficiency in LO-FGR may not be reflected in the Doppler examination of the umbilical artery (UA). Recent studies have shown that Doppler ultrasonography performed in other vascular regions, such as the brain and uterine arteries, may be more important in detecting LO-FGR that cannot be identified through the Doppler examination of the UA (6). In LO-FGR, adaptive changes in the cerebral circulation (brain-sparing effect) occur as a result of low resistance to flow in the middle cerebral artery (MCA) (7). Apart from the formation of brain-sparing effects, there is little literature information concerning the diagnostic and predictive value of the Doppler examination of the femoral artery (FA) among peripheral arteries. Some animal experimental studies have investigated the effects of the Doppler examination of the FA in the presence of hypoxia (8, 9). However, only a few studies have performed the Doppler examination of the FA in patients with FGR (10), and there is still an open debate as to which Doppler parameter indicates a progressive or stable fetal state in LO-FGR cases.

In this study, we investigated the utility of Doppler ultrasonography measurements in the diagnosis of cases with LO-FGR. The primary endpoint of the study was the importance of ultrasonographic Doppler parameters in the diagnosis and follow-up of patients with LO-FGR. The secondary endpoint was the ability of the FA Doppler measurements and other Doppler markers to predict adverse perinatal outcomes in patients with LO-FGR.

Material and Method

This prospective case-control study was conducted from April 2022 to April 2023 at the perinatology clinic of Ankara City Hospital. Written informed consent was obtained from all participants. Research and publication ethics were complied with in our article. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Number 2 Medical Research Ethics Unit of the Ankara City Hospital (Number: E2-22-2674, Date: 26/10/2022).

Study population

The study included 168 cases, including 83 pregnancies presenting with late-onset FGR (LO-FGR) and 85 healthy singleton pregnancies. All pregnancies were past the 32nd gestational week. The LO-FGR cases were further divided into two groups according to the requirement of admission to the neonatal intensive care unit (NICU) (15 with and 68 without this requirement). The control group was selected from pregnant women with similar characteristics in terms of body mass index (BMI) and gestational week. Pregnant women with chronic lung and heart diseases, hypertensive diseases of pregnancy, chronic kidney and liver diseases, systemic diseases, or a history of malignancy were excluded from the study. Furthermore, twin pregnancies and pregnant women with fetal structural and chromosomal disorders were not included in the study. Cases that met the FGR criteria specified in the Society for Maternal-Fetal

Medicine (SFMF) guidelines were included in the study. Accordingly, fetal growth restriction was defined as the estimated fetal weight (EFW) or abdominal circumference (AC) in the ultrasonographic evaluation below the 10th percentile for gestational age. Cases with FGR criteria at and after 32 weeks of gestation were accepted as LO-FGR (11). Gestational age was confirmed using first-trimester ultrasound findings or the date of the last regular menstrual period.

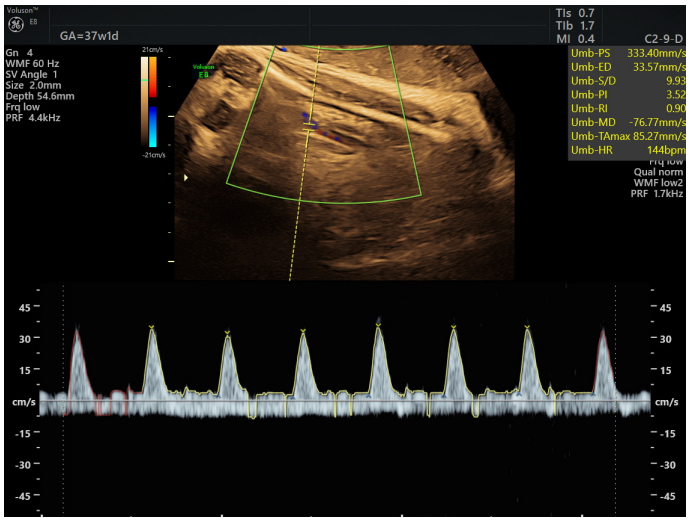
Ultrasonography

Sonographic evaluations of all participants were performed using the Voluson E8 ultrasound device (GE Healthcare, Milwaukee, WI) with a 3.5-MHz convex transducer (6C1-PVT-375BT) transabdominal probe. Fetal biometric measurements were undertaken by measuring head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL). EFW and percentile ratios were calculated according to the formula of Hadlock et al. (12). In all fetuses, Doppler examinations of the UA, MCA, uterine artery (UtA), and FA were undertaken. The cerebroplacental ratio (CPR) was obtained by dividing the pulsatility index (PI) of the MCA by the pulsatility index of the UA (MCA PI / UA-PI). The cerebroplacental-uterine ratio (CPUR) was determined as the ratio of the CPR measurement to the UtA PI (13). The measurements of the FA were made by performing Doppler ultrasonography on the lower extremity, where the femoral bone closest to the ultrasound probe was clearly visualized. The angle between the transducer and the bone was set to 45° or less (Figure 1). All other ultrasonographic Doppler measurements were undertaken by an experienced sonographer in accordance with standard recommendations.

Statistical Analysis

SPSS version 22 (IBM, Chicago, IL, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used to determine whether the data complied with a normal distribution. After it was determined that the data did not conform to a normal distribution, the Mann-Whitney U test was conducted for the comparison between the two groups. The chi-square test was used when examining categorical variables. $p<0.05$ was considered statistically significant.

Figure I. This Doppler image shows the technique of measuring blood flow of the femoral artery in the fetal lower extremity, where the femoral bone is clearly visible. The measurement was taken at 37+1 weeks.



Results

The study included 168 pregnancies, of which 83 presented with LO-FGR and 85 were healthy controls. (Table I) shows the demographic data and ultrasonography parameters of all participants. Age, BMI, gravida, parity, and gestational week were similar between the two groups. Among the ultrasound parameters, the UtA PI, systolic/diastolic ratio (S/D) of the UA, peak systolic volume (PSV) of the MCA, and multiples of median (MoM) of the MCA PSV were also similar. However, the LO-FGR group had significantly lower MCA PI and FA PI values ($p<0.001$ and $p=0.002$, respectively) and a statistically higher UA PI measurement ($p=0.048$). In addition, CPR and CPUR were statistically significantly lower in the LO-FGR group ($p<0.001$ and $p=0.018$, respectively).

The 83 cases with LO-FGR in the study group were further divided into two groups according to the NICU requirements. While 15 newborns were admitted to NICU, 68 did not require intensive care. The ultrasonography parameters and perinatal

outcomes of the patients according to the NICU requirements are given in (Table II). The UA Doppler, UtA Doppler, MCA Doppler, and FA PI measurements were similar between these two groups. However, EFW, birth week, and birth weight were significantly lower in the NICU group (*p=0.033*, *p=0.013*, and *p=0.006*, respectively). Lastly, the rate of cases with an Apgar score of <7 at the first minute was 46.7% in the NICU group and 7.4% in the group that did not require neonatal intensive care (*p<0.001*).

Table I. Comparison of the demographic data and ultrasound parameters of the groups.

	Late-onset FGR (n = 83)	Control (n = 85)	*p value*
Age (years)	27 (6)	28 (8.5)	*0.695*
BMI (kg/m^2)	27.5 (3.7)	27.5 (4)	*0.726*
Gravida	2 (2)	2 (2)	*0.560*
Parity	0 (1)	1 (1)	*0.864*
Abortion	0 (1)	0 (1)	*0.474*
Gestational week[a]	37 (2)	36 (2)	*0.263*
EFW (grams)	2281 (451)	2482 (695.5)	***<0.001***
Placental localization, n (%)			
Anterior	40 (48.2%)	41 (48.2%)	*0.996*
Posterior	43 (51.8%)	44 (51.8%)	
UtA PI	0.7 (0.4)	0.7 (0.4)	*0.153*
UA S/D	2.6 (0.6)	2.4 (0.6)	*0.063*
UA PI	1.0 (0.2)	0.9 (0.3)	***0.048***
MCA PSV	49 (15.8)	47 (15)	*0.633*
MCA PSV MoM	0.9 (0.3)	0.9 (0.3)	*0.829*
MCA PI	1.5 (0.6)	1.9 (0.8)	***<0.001***
FA PI	4.5 (1)	4.1 (1.3)	***0.002***
CPR	1.6 (0.7)	2.1 (1)	***<0.001***
CPUR	2.3 (1.8)	2.8 (2)	***0.018***

(FGR: fetal growth restriction, BMI: body mass index, kg: kilogram, m^2: square meters, EFW: estimated fetal weight, UtA: uterine artery, PI: pulcatility index, UA: umbilical artery, S/D: systole/diastole, MCA: middle cerebral artery, PSV: peak systolic velocity, MoM: multiples of median, FA: femoral artery, CPR: cerebroplacental ratio, CPUR: cerebroplacental-uterine ratio)

[a]Gestational week at which ultrasonographic evaluation was made.

Data presented as median (interquartile range) or count (percentage). *p<0.05* accepted as statistically significant.

Discussion

This prospective study evaluated the relationship between FA Doppler measurements and poor perinatal outcomes in pregnant women presenting with FGR. The results showed that the FA PI value was higher in the FGR cases than in the controls. We also found that the FA PI value was similar between those with and without the NICU requirement among the FGR cases.

There is no gold standard definition for FGR. In most studies, FGR is defined as the estimated fetal weight <10th percentile. In the Delphi consensus published in 2016, a differentiation was made between early- and late-onset FGR by taking 32 weeks of gestation at a cut-off value in the absence of congenital anomalies. For late-onset FGR, if AC/EFW is <3rd percentile or AC/EFW is <10th percentile, the UA PI or UtA PI is defined as >95th percentile or CPR <5th percentile (14).

Late-onset FGR (LO-FGR) represents 70–80% of all FGR cases (15). Studies have shown that UA can identify severe placental insufficiency but fails to detect mild cases of placental insufficiency in LO-FGR. In addition, LO-FGR has no natural history, and these patients can experience rapid worsening without ultrasonographic findings (16, 17). Other fetal vascular Doppler assessments, including those of the UtA and MCA, have been recommended since UA Doppler cannot provide definitive findings for the identification of LO-FGR cases (17).

Only a few studies have performed the Doppler examination of peripheral arteries in patients with FGR. Peripheral blood vessels of fetuses with FGR may be deficient in nutrients and oxygen (18). In a study that conducted the Doppler examination of the tibial artery in patients with LO-FGR, the findings obtained from this examination were reported to be associated with adverse perinatal outcomes, such as acidemia and respiratory requirements (19). The

first study on the Doppler examination of the FA in FGR cases was conducted in 1991, in which the FA PI measurement was observed to increase linearly as the gestational week of the cases progressed, and two fetuses with FGR had abnormal FA Doppler findings died after birth (20). Another study found that acute hypoxemia in healthy fetuses caused a sudden decrease in both fetal heart rate and blood flow to the FA (21). In a study evaluating 221 patients, a high resistance pattern was observed in FA Doppler examinations throughout pregnancy (22). Due to the brain-sparing effect in FGR cases, Doppler examinations of the extremities have also attracted the attention of researchers. In the current study, we also observed a higher FA PI measurement in the LO-FGR cases than in the controls. However, in the LO-FGR group, the FA Doppler measurements of the cases with and without the NICU requirement were similar; therefore, these measurements did not have any utility in predicting adverse perinatal outcomes in patients with FGR.

Many research initiatives have focused on establishing good diagnostic markers for FGR and predictive models for adverse outcomes in FGR based on Doppler ultrasound findings (23) Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clx00ED;nic and Hospital Sant Joan de Deu. The PORTO study suggested that functional parameters were required to predict poor perinatal outcomes in FGR (24). Although there is an association between abnormal MCA PI measurements and poor perinatal outcomes, it remains unclear whether preterm delivery provides any benefit. It has been reported that in 25% of LO-FGR cases, the MCA PI is <5th percentile, suggesting chronic hypoxia (16). On the other hand, a reduced PI in the MCA is also associated with poor perinatal outcomes and an increased risk of abnormal neurodevelopment (25). Similar to previous studies, we also determined the MCA PI to be lower in the LO-FGR cases compared to the controls. However, we did not observe any difference in the MCA PI between the cases with and without NICU requirements.

Table II. Comparison of demographic data, ultrasound parameters, and delivery outcomes according to NICU requirement among patients with late-onset FGR.

NICU requirement	NICU (n = 15)	No NICU (n = 68)	*p value*
Age (years)	28 (8)	27 (6)	*0.502*
BMI (kg/m^2)	27.6 (5)	27.4 (3.7)	*0.670*
Gravida	2 (1)	2 (2)	*0.421*
Parity	0 (1)	1 (1)	*0.208*
Abortion	0 (1)	0 (0.8)	*0.565*
Gestational week[a]	36 (3)	37 (2)	*0.115*
EFW (grams)	1918 (810)	2340 (427.8)	***0.033***
Placental localization, n (%)			*0.114*
Anterior	10 (66.7%)	30 (44.1%)	
Posterior	5 (33.3%)	38 (55.9%)	
UtA PI	0.7 (0.8)	0.7 (0.4)	*0.740*
UA S/D	2.5 (1.3)	2.6 (0.6)	*0.925*
UA PI	0.9 (0.4)	1 (0.2)	*0.772*
MCA PSV	49.9 (12.4)	49 (16.5)	*0.683*
MCA PSV MoM	0.9 (0.2)	0.9 (0.3)	*0.329*
MCA PI	1.5 (0.6)	1.5 (0.6)	*0882*
FA PI	4.7 (1.3)	4.5 (1)	*0.356*
CPR	1.6 (1.3)	1.6 (0.6)	*0.934*
CPUR	2.5 (3.2)	2.3 (1.7)	*0.714*
Delivery week	37 (3)	38 (1)	***0.013***
Mode of delivery, n (%)			*0.458*
Cesarean section	11 (73.3%)	43 (63.2%)	
Vaginal delivery	4 (26.7%)	25 (36.8%)	
Birth weight (grams)	2200 (710)	2405 (472.5)	***0.006***
Apgar score <7 at the first minute	7 (46.7%)	5 (7.4%)	***<0.001***
Apgar score <7 at the fifth minute	1 (6.7%)	0 (0%)	*0.181*

(BMI: body mass index, kg: kilogram, m^2: square meters, EFW: estimated fetal weight, UtA: uterine artery, PI: pulcatility index, UA: umbilical artery, S/D: systole/diastole, MCA: middle cerebral artery, PSV: peak systolic velocity, MoM: multiples of median, FA: femoral artery, CPR: cerebroplacental ratio, CPUR: cerebroplacental-uterine ratio)

[a]Gestational week at which ultrasonographic evaluation was made.

Data presented as median (interquartile range) or count (percentage). *p<0.05* accepted as statistically significant.

CPR, defined as the ratio of the MCA PI measurement to the UA PI measurement, has been shown to be more sensitive to hypoxia than its individual components (26). CPR is important in the management of LO-FGR because it helps predict adverse perinatal outcomes (27). Twenty to twenty-five percent of LO-FGR cases have abnormal CPR values before birth and have a higher rate of adverse outcomes (28, 29). In the current study, CPR was significantly lower in the FGR group than in the control group. However, CPR did not significantly differ according to the NICU requirement among the LO-FGR cases.

CPUR, obtained by adding the UA PI to the CPR value, has been investigated in terms of its ability to predict adverse perinatal outcomes. In a study of 891 fetuses, the addition of the UA Doppler to the CPR parameter did not result in any predictive improvement (30). In another study, CPUR was found to detect more FGR cases than any other measured Doppler parameter (31). A study examining the prognostic effects of LO-FGR in 114 patients reported that CPUR was independently associated with adverse outcomes (32). In the current study, the CPUR value was lower in the LO-FGR group compared to the control group. However, we did not observe any differences between the LO-FGR subgroups in terms of the prognostic value of CPUR.

Another predictor of poor perinatal outcomes among LO-FGR cases is a very small EFW. Among fetuses below the 10th percentile, those with an EFW of <3rd percentile have a much higher risk of adverse perinatal outcomes, independent of their CPR and UtA Doppler values (15). A study conducted with pregnant women with LO-FGR found that adverse perinatal outcomes increased as birth weight decreased (32). In our cases of LO-FGR, newborns requiring NICU had a statistically lower EFW. Although Doppler parameters are normal, the success of EFW alone in showing adverse perinatal outcomes, especially in LO-FGR cases, seems to be effective.

The relatively small sample size and single-center design of the study can be counted among its limitations. Another limiting factor was that we did not include the long-term outcomes of the newborns. In addition, femoral artery Doppler measurements were not performed intermittently. The strength of the study is its prospective design. Multicenter studies with larger samples are needed.

Inconclusion, this study showed that the FA PI measurement was higher in the late-onset FGR cases than in the healthy controls. However, Doppler examination of the FA was not found to be effective in demonstrating adverse perinatal outcomes. There is a need for multicenter studies to demonstrate the importance of the FA Doppler examination in patients with FGR and determine its utility in the prediction of adverse perinatal outcomes.

References

1. Lackman F, Capewell V, Gagnon R, Richardson B. Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. American journal of obstetrics and gynecology 2001;185(3):674-682.

2. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. Clin Med Insights Pediatr 2016;10:67-83.

3. Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound in obstetrics & gynecology 2013;42(4):400-408.

4. Aviram A, Sherman C, Kingdom J, Zaltz A, Barrett J, Melamed N. Defining early vs late fetal growth restriction by placental pathology. Acta Obstet Gynecol Scand 2019;98(3):365-373.

5. Crovetto F, Triunfo S, Crispi F, et al. First-trimester screening with specific algorithms for early-and late-onset fetal growth restriction. Ultrasound in obstetrics & gynecology 2016;48(3):340-348.

6. Severi FM, Bocchi C, Visentin A, et al. Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet

Gynecol 2002;19(3):225-228.
7. Crovetto F, Crispi F, Scazzocchio E, et al. First-trimester screening for early and late small-for-gestational-age neonates using maternal serum biochemistry, blood pressure and uterine artery Doppler. Ultrasound Obstet Gynecol 2014;43(1):34-40.
8. Muijsers GJ, van Huisseling H, Hasaart TH. The effect of maternal hypoxemia on the umbilical and femoral artery blood flow velocity waveforms and the relationship with mean arterial pressure in fetal sheep. Gynecol Obstet Invest 1993;35(1):1-6.
9. Iversen NK, Wang T, Baatrup E, Crossley DA, 2nd. The role of nitric oxide in the cardiovascular response to chronic and acute hypoxia in White Leghorn chicken (Gallus domesticus). Acta Physiol (Oxf) 2014;211(2):346-357.
10. Manabe A, Hata T, Kitao M. Longitudinal Doppler ultrasonographic assessment of alterations in regional vascular resistance of arteries in normal and growth-retarded fetuses. Gynecol Obstet Invest 1995;39(3):171-179.
11. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol 2020;223(4):B2-b17.
12. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181(1):129-133.
13. Graupner O, Meister M, Lecker L, Carow J, et al. Role of the cerebro-placental-uterine ratio in predicting adverse perinatal outcome in low-risk pregnancies at term. Arch Gynecol Obstet 2022 Aug 30.
14. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48(3):333-339.
15. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound Obstet Gynecol 2012;39(3):299-303.
16. Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2011;37(2):191-195.
17. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther 2014;36(2):86-98.
18. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol 2018;49:53-65.
19. Norvilaitė K, Ramašauskaitė D, Bartkevičienė D, Šliachtenko A, Kurmanavičius J. Fetal Tibial Artery Doppler in Late IUGR Fetuses: A Longitudinal Study. Journal of clinical medicine 2023;12(1):82.
20. Mari G. Arterial blood flow velocity waveforms of the pelvis and lower extremities in normal and growth-retarded fetuses. Am J Obstet Gynecol 1991;165(1):143-151.
21. Martin CB Jr. Normal fetal physiology and behavior, and adaptive responses with hypoxemia. Semin Perinatol 2008 Aug;32(4):239-242.
22. Morales-Roselló J, Diaz García-Donato J. Study of fetal femoral and umbilical artery blood flow by Doppler ultrasound throughout pregnancy. Arch Gynecol Obstet 1999;262(3-4):127-131.
23. Triunfo S, Parra-Saavedra M, Rodriguez-Sureda V, et al. Angiogenic Factors and Doppler Evaluation in Normally Growing Fetuses at Routine Third-Trimester Scan: Prediction of Subsequent Low Birth Weight. Fetal Diagn Ther 2016;40(1):13-20.
24. Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208(4):290.e1-6.
25. Strigini FA, De Luca G, Lencioni G, Scida P, Giusti G, Genazzani AR. Middle cerebral artery velocimetry: different clinical relevance depending on umbilical velocimetry. Obstet Gynecol 1997;90(6):953-957.
26. Baschat AA, Gembruch U. The cerebroplacental

Doppler ratio revisited. Ultrasound Obstet Gynecol 2003;21(2):124-127.
27. Monteith C, Flood K, Pinnamaneni R, et al. An abnormal cerebroplacental ratio (CPR) is predictive of early childhood delayed neurodevelopment in the setting of fetal growth restriction. Am J Obstet Gynecol 2019;221(3):273.e1-.e9.
28. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol 2011;117(3):618-626.
29. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Puerto B, Gratacós E. Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by fractional moving blood volume. Am J Obstet Gynecol 2010;203(1):42.e1-6.
30. Morales-Roselló J, Buongiorno S, Loscalzo G, Abad García C, Cañada Martínez AJ, Perales Marín A. Does Uterine Doppler Add Information to the Cerebroplacental Ratio for the Prediction of Adverse Perinatal Outcome at the End of Pregnancy? Fetal Diagn Ther 2020;47(1):34-44.
31. MacDonald TM, Hui L, Robinson AJ, et al. Cerebral-placental-uterine ratio as novel predictor of late fetal growth restriction: prospective cohort study. Ultrasound Obstet Gynecol 2019;54(3):367-375.
32. Yang Z, Lv W, Zhao B, Yao J, Yang Y, Yin Z. Uteroplacental-Cerebral Ratio: A Doppler Parameter for Prognostic Prediction of Late-Onset Fetal Growth Restriction: Single Center Prospective Cohort Study. J Clin Med 2022;12(1).

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Can HCG MoM Ratio Predict Preeclampsia?

HCG MoM Oranı Preeklempsiyi Predikte Eder mi?

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Can HCG MoM Ratio Predict Preeclampsia?

Abstract

Objective: To predict preeclampsia by the ratio of the HCG MoM value in the first and second trimester screening tests.

Material and Method: The HCG-MoM values of 136 pregnant women with preeclampsia and 222 normatensive pregnant women used for first and second-trimester screening tests were proportioned , and the difference between the groups was examined. Numeric variables are expressed as mean ± standard deviation, median (minimum – maximum), and categorical variables as n (%).

Results: HCG MoM values were not different between the two groups and were within the accepted international values.The ratio of the free HCG MoM value in the first trimester to the intact HCG MoM value in the second trimester was significantly higher in the control group (1.06) than in the study group (0.99) (*p=0.02*).

Conclusion: Rating the MoM values of β-HCG, a biochemical marker used in screening tests for chromosomal anomaly, may predict preeclampsia in the later weeks of pregnancy.

Keywords: HCG MoM, preeclampsia, screening tests.

Özet

Amaç: Birinci ve ikinci trimester tarama testlerindeki HCG MoM değerinin oranına göre preeklampsiyi öngörmek.

Gereç ve Yöntem: 136 preeklampsili gebe ile 222 normal tansiyonlu gebenin birinci ve ikinci trimester tarama testleri için kullandıkları HCG-MoM değerleri oranlanarak gruplar arasındaki fark incelendi. Sayısal değişkenler ortalama ± standart sapma, medyan (minimum – maksimum), kategorik değişkenler ise n (%) olarak ifade edilmiştir.

Bulgular: İki grup arasında HCG MoM değerleri arasında fark izlenmedi ve kabul edilen uluslararası değerler içerisindeydi. Birinci trimesterdeki serbest HCG MoM değerinin, ikinci trimesterdeki intakt HCG MoM değerine oranı kontrol grubunda (1,06) çalışma grubuna göre (0,99) anlamlı olarak yüksekti (*p=0,02*).

Sonuç: Kromozomal anomali tarama testlerinde kullanılan biyokimyasal bir belirteç olan β-HCG'nin MoM değerlerinin derecelendirilmesi, gebeliğin ileri haftalarında preeklampsiyi öngörebilir.

Anahtar Sözcükler: HCG MoM, preeklampsi, tarama testleri.

Introduction

Gestational diseases in pregnancy are a spectrum of diseases thought to be due to abnormal trophoblast invasion and placental ischemia. (1). Preeclampsia is a multisystemic disorder that affects both the mother and the newborn (2). The pathophysiology of preeclampsia involves an implantation abnormality of the placenta and an abnormal maternal response to factors released from the placenta (3). According to the two-wave theory of endovascular trophoblast migration in pregnancy, trophoblast migration occurs in the first trimester to the decidual segment of the spiral arteries and in the early second trimester to the myometrial segment (4). This migration is necessary to reduce resistance and increase blood flow in the uteroplacental bed during pregnancy.

However, in preeclamptic women it has been observed that the spiral arteries in the myometrial part of the placental bed do not undergo the physiological change mentioned above, and it is known that this situation becomes evident in the early second trimester (5). Human chorionic gonadotropin (HCG) is also produced from the trophoblastic tissue that makes this change.

It is known that the HCG multiple of the median (MoM) may be different in screening tests performed in the early second trimester in preeclampsia (6-8). Therefore, the change in HCG MoM values can be used as a valuable marker for preeclampsia. Because of the unique capacity of each placenta to produce HCG, the ratio between these two values may better predict preeclampsia than individual HCG-MoM values measured during double and triple screening. In this study, we hypothesise that HCG decline on screening tests will be different in pregnancies that will develop preeclampsia in the future compared with normal pregnancies. Our aim was to determine the relationship between MoM levels of free and intact HCG and the ratio of these two tests used in screening tests and preeclampsia" and their predictive power.

Material and Method

This retrospective observational study included pregnant women who presented to the tertiary center outpatient clinic between 2010 and 2020 and underwent both double and triple screening in the same pregnancy. Patient records and hospital databases were used for data collection. Patient demographic characteristics, clinical features, prenatal follow-up, and fetal chromosomal diagnosis were evaluated. Multiple pregnancies, women who did not have double and triple screening in the same pregnancy, women in whom fetal death occurred before 22 weeks of gestation, or whose fetuses were found to have chromosomal abnormalities or other structural malformations were excluded from the study. The MOM value of free β-HCG in pregnancies subjected to screening for aneuploidy in the first trimester between 11-13+6 weeks of gestation, and in the same pregnancy, the MOM values of intact HCG measured during triple screening between 15-17+6 weeks of gestation were determined by a certified laboratory. 136 pregnancies with preeclampsia in the study group and 222 pregnancies with normal blood pressure in the control group were analyzed. Preeclampsia was defined as new-onset hypertension after 20 weeks of gestation in a previously normotensive woman (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHG and proteinuria (presence of protein ≥0.3 g in a 24-hour urine sample), or new-onset hypertension and the presence of end-organ dysfunction with or without proteinuria.
Approval was obtained from the ethics committee before starting the study (2021-08-TUEK approval).

Statistical Analysis

All statistical analyzes were performed with the SPSS 20.0 package program (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to confirm the normal distribution of continuous numerical variables. Numeric variables are expressed as mean ± standard deviation, median (minimum – maximum), and categorical variables as n (%). Pearson's chi-square test was used to compare categorical variables.

Bivariate correlation analysis was used to determine the correlation ratio between bHCG and intact HCG measured during double and triple screening, and Spearman's coefficient was used for evaluation. A p value less than 0.05 was considered statistically significant.

Results

The study involved 136 pregnant women with preeclampsia (study group) and 222 normotensive pregnant women (control group). While the average age of the patients in the preeclamptic group was 31 years, it was 27 years in the control group. The average age and body mass index of pregnant women in the study group was statistically significantly higher than in the control group ($p<0.05$). %25 (n=35) of patients in the study group and %32 (n=73) of patients in the control group were primiparous. There was no significant difference between the two groups in primiparity ($p=0.09$) and use of assisted reproductive techniques ($p=1$). %74 (n=103) of the study group and %28 (n=28) of the control group were delivered by cesarean section. The cesarean section rate was statistically significantly higher in the study group than in the control group ($p<0.05$). (Table I).

Table I. Characteristics of the Patients

Characteristics	Study group (%) (n=136)	Control group (%) (n=222)	*p value*
Age	31±6	27±5	*0.000**
Primiparity	35 (%25.7)	73 (%32.9)	*0.09*
BMI (kg/m^2)	32±4.7	28±3.7	*0.000**
Smoking	18(%13)	11(%5)	*0.005**
ART	3(%2.2)	5/(%2)	*1.00*
CS delivery	103(%74,3)	28(%12.6)	*0.000**

Values were presented as mean±standart deviation

BMI:Body Mass İndex

ART: Assisted reproductive technologies

CS: Cesarean section

*: statistically significant

There was no statistically significant difference between the study and control groups in free HCG MoM levels measured in the first trimester ($p=0.139$), intact HCG MOM level measured during the triple screening test ($p=0.977$), PAPP-A MOM level ($p=0.244$), AFP MOM level ($p=0.21$), and E3 MOM level ($p=0.92$). The ratio of the free bHCG MOM value in the second trimester to the intact HCG MOM value measured in the third trimester was significantly higher in the control group than in the study group ($p=0.02$). Biochemical marker values are given in (Table II) in two groups.

Table II. Biochemical Marker Values

Values	Study group (n=136)	Control group (n=222)	*p value*
Hcg MoM (first trimester)	1.02±0.53	0.98±0.61	*0.139*
Hcg MoM (second trimester)	1.07±0.59	1.13±0.85	*0.977*
Ratio	1.06±0.47	0.99±0.49	*0.02**
PAPP-A MoM	0.91±0.49	1.09±0.61	*0.056*
AFP MoM	1.1±0.38	1.17±0.54	*0.21*
E3 MoM	1.09±0.33	1.05±0.36	*0.92*

Values were presented as mean±standart deviation

PAPP-A: Pregnancy Associated Plasma Protein

AFP: Alpha-fetoprotein

E3:Estriol

The relationship between the HCG-MoM level measured in the first trimester screening test (mean: 1.0, SD: 0.56) and the HCG-MoM level measured in the second trimester screening test (mean: 1.09, SD: 0.70) was measured by Pearson correlation ($r(356)=0.69$, $p<0.05$). A moderate, positive and significant relationship was found between these variables. The results of the correlation analysis are shown in (Table III).

Table III. First and Second Trimester HCG MoM Bivariable Correlation Analysis

HCG MoM (first trimester)	Pearson Correlation Sig. (2-tailed) N	1 . 358	0.695* .001 358
HCG MoM (Second trimester)	**Pearson Correlation** **Sig. (2-tailed)** **N**	**0.695** **.000** **358**	**1** **.** **358**

HCG MoM (first trimester) HCG MoM (Second trimester)

Discussion

HCG becomes positive in maternal blood one day after implantation. A dysregulation of HCG, which has numerous functions such as implantation, progesterone production, angiogenesis, and trophoblastic differentiation, leads to adverse pregnancy outcomes. Previous studies have emphasized that there is a close relationship between preeclampsia and immune response and angiogenesis (9). HCG plays a key role here and is produced almost exclusively in the placenta, while a very small proportion is produced in the fetal kidneys (10). In hypertensive pregnancy diseases, the clinic develops after the 20th week, so it is useful to look for HCG, which is almost completely released from the placenta, as a biomarker for predicting these placenta-related diseases.

Although there are many studies in the literature investigating the association between HCG and some other biomarkers and preeclampsia, it is noteworthy that their results are contradictory. The risk factors for the condition have been described in detail in the literature, including advanced maternal age, ART, smoking, and increased BMI (11). In this study, the same risks, with the exception of ART, were also statistically higher in preeclamptic pregnancies. On the other hand, pregnant women who will develop preeclampsia were found to have lower than normal free HCG levels in the first trimester compared with normal pregnancies (12-14). In contrast to these studies, Honarjoo et al's study of 4605 pregnant women showed that high free HCG levels (3 MoM and above) would cause a 5.65-fold increase in the first trimester (15). In their study of 155 patients, Mikat et al. found that serum β-HCG levels were significantly higher in pregnancies that would later develop preeclampsia (16). In the meta-analysis by Liu et al. it was found that the MoM value of serum β-HCG level was significantly higher in preeclamptic pregnancy than in normal pregnancy (17). In contrast to these studies, the study by Gomes et al argued that b-HCG levels were not associated with preeclampsia (18). Similarly, in our study, we found that free β-HCG level and β- HCG MOM value in the first trimester were not associated with preeclampsia (*p=0.139*). Regardless of preeclampsia, each placenta has its own potential to produce HCG, and its levels may vary independently of preeclampsia.

In this case, in preeclampsia, the HCG production capacity of the placenta is impaired in the early second trimester, the time of triple screening. We expect that HCG MoM change levels will be different in pregnancies that will develop pre-eclampsia in the future compared to normal pregnancies. If hCG reflects placental function and quality, it is reasonable to associate preeclampsia with low hCG levels, but considering that sprial artery remodeling occurs between 12-16 weeks of gestation, it is possible that the levels measured HCG MOM in the double and triple screening tests do not yet reflect the pathophysiology of preeclampsia. The lack of association between double- and triple-screening HCG MoM levels and preeclampsia in our study may be attributed to the unique HCG production of each placenta, but we hypothesised that HCG production decreases more in preeclampsia because of placental ischemia. For this reason, it was found that the ratio of HCG MoM values in pregnant women with preeclampsia as opposed to HCG MoM values was statistically higher in double and triple screening than in normatensive pregnant women (*p=0.02*).

There are a limited number of studies in the

literature on HCG levels in double and triple screening tests and the relationship between them. Sharony et al. investigated the relationship between free β-HCG in the first trimester and intact β-HCG in the second trimester in the same pregnant woman and analyzed the relationship between the increase in free beta-HCG levels (fbhCG) and pregnancy complications (PC), fetal growth restriction (FGR), and preeclampsia. As a result of this study, no association was found between first trimester fbhCG and FGR and between fbhCG and ihCG and PE (19). In our study, we could not demonstrate any association between intact HCG and free HCG and preeclampsia. However, in contrast to Sharony's study, the bivariable correlation analysis performed in our study found that the HCG MOM values measured in double scan and triple scan were correlated ($p<0.001$). We assume that each placenta in each pregnancy has its own unique ability to produce HCG, so HCG levels may also be correlated in double and triple screening.

Because of the unclear pathophysiology in the prevention of preeclampsia, treatment options in current medicine are limited. It has been observed that aspirin taken before 16 weeks of gestation effectively prevents preeclampsia (20). We believe that the mortality and morbidity of preeclampsia can be reduced by calculating the HCG-MoM ratio and initiating aspirin therapy. Our study is a non-randomized retrospective study. We could not determine a predictive value for the HCG-MoM ratio. The strength of the study is that it is a homogeneous group and it is the first study in this field in the literature.

Conclusion

Consequently, dysregulation of hCG secretion adversely affects pregnancy outcome. Assessment of MoM levels of β-HCG, a biochemical marker used in screening tests for chromosomal abnormalities, may predict preeclampsia in the later weeks of pregnancy. We believe that the mortality and morbidity of preeclampsia can be reduced by assessing risk factors, which can be done within these weeks, calculating the ratio of HCG-MoM levels, and starting aspirin therapy.

References

1. Obstetricians ACo, Gynecologists. ACOG practice bulletin no. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133:e1-e25.
2. Lim R, Barker G, Lappas M. TREM-1 expression is increased in human placentas from severe early-onset preeclamptic pregnancies where it may be involved in syncytialization. Reproductive Sciences. 2014;21:562-572.
3. Rolfo A, Giuffrida D, Nuzzo AM. et al. Pro-inflammatory profile of preeclamptic placental mesenchymal stromal cells: new insights into the etiopathogenesis of preeclampsia. PLoS One. 2013;8:e59403.
4. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta. 2006;27:939-958.
5. Suri S, Muttukrishna S, Jauniaux E. 2D-ultrasound and endocrinologic evaluation of placentation in early pregnancy and its relationship to fetal birthweight in normal pregnancies and pre-eclampsia. Placenta. 2013;34:745-750.
6. Cole LA. New discoveries on the biology and detection of human chorionic gonadotropin. Reproductive Biology and Endocrinology. 2009;7:1-37.
7. Zhang X, Huangfu Z, Shi F, Xiao Z. Predictive Performance of Serum β-hCG MoM Levels for Preeclampsia Screening: A Meta-Analysis. Frontiers in Endocrinology. 2021;12.
8. Cole LA. Biological functions of hCG and hCG-related molecules. Reproductive Biology and Endocrinology. 2010;8:1-14.
9. Toldi G, Švec P, Vásárhelyi B. et al. Decreased number of FoxP3+ regulatory T cells in preeclampsia. Acta obstetricia et gynecologica Scandinavica. 2008;87:1229-1233.
10. Fournier T, Guibourdenche J, Evain-Brion D. hCGs: different sources of production, different glycoforms and functions. Placenta. 2015;36:S60-S5.
11. Cincotta R, Brennecke S. Family history of

pre-eclampsia as a predictor for pre-eclampsia in primigravidas. International Journal of Gynecology & Obstetrics. 1998;60:23-27.
12. Abdel Moety GAF, Almohamady M, Sherif NA. et al. Could first-trimester assessment of placental functions predict preeclampsia and intrauterine growth restriction? A prospective cohort study. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;29:413-417.
13. Johnson M, Riddle A, Grudzinskas J, Sharma V, Collins W, Nicolaides K. The role of trophoblast dysfunction in the aetiology of miscarriage. BJOG: An International Journal of Obstetrics & Gynaecology. 1993;100:353-359.
14. Di Lorenzo G, Ceccarello M, Cecotti V. et al. First Trimester Maternal Serum PlGF, Free β-hCG, PAPP-A, PP-13, Uterine Artery Doppler and Maternal History for the Prediction of Preeclampsia. Obstetrical & Gynecological Survey. 2012;67:623-624.
15. Honarjoo M, Kohan S, Zarean E, Tarrahi MJ. Assessment of β-human-derived chorionic gonadotrophic hormone [βhCG] and pregnancy-associated plasma protein A [PAPP-A] levels as predictive factors of preeclampsia in the first trimester among Iranian women: a cohort study. BMC pregnancy and childbirth. 2019;19:1-5.
16. Mikat B, Zeller A, Scherag A, Drommelschmidt K, Kimmig R, Schmidt M. βhCG and PAPP-A in first trimester: predictive factors for preeclampsia? Hypertension in Pregnancy. 2012;31:261-267.
17. Liu H-Q, Wang Y-H, Wang L-L, Hao M. Predictive value of free β-hCG multiple of the median for women with preeclampsia. Gynecologic and Obstetric Investigation. 2016;81:137-147.
18. Gomes MS, Carlos-Alves M, Trocado V, Arteiro D, Pinheiro P. Prediction of adverse pregnancy outcomes by extreme values of first trimester screening markers. Obstetric medicine. 2017;10:132-137.
19. Sharony R, Sharon-Weiner M, Kidron D. et al. The association between maternal serum first trimester free βhCG, second trimester intact hCG levels and foetal growth restriction and preeclampsia. Journal of Obstetrics and Gynaecology. 2018;38:363-366.
20. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. American Journal of Obstetrics and Gynecology. 2020.

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The Effect Of Vitamin D Levels On Eradication Of Helicobacter Pylori Infection

Helicobacter Pilori Eradikasyonunda D Vitamini Düzeylerinin Etkisi

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The Effect Of Vitamin D Levels On Eradication Of Helicobacter Pylori Infection

Abstract

Objective: Many factors are known to play a role in the eradication of Helicobacter pylori (Hp). The aim of this study is to investigate the effect of 25(OH) vitamin D levels on the success of H. pylori eradication.

Material and Method: This retrospective study included 237 patients, aged 18-85 years, who presented at the Gastroenterology Polyclinic with dyspeptic complaints which had been ongoing for at least 6 months. Patients were divided into two groups according to their 25(OH) vitamin D level as >20ng/ml and <20ng/ml. For Hp eradication, the patients were administered treatment of 1x1 320 mg gemifloxacin, 2x1 1 gr amoxicillin, and 1 x1 40 mg rabeprazole. After 1 month of treatment, faecal examination was made to determine whether or not Hp was eradicated. The eradication rates were compared between the groups with high and low level 25(OH) vitamin D.

Results: The patients comprised 139 (58.6%) females and 98 (41.4%) males with a mean age of 40.9±14.1 years (range, 18-72 years). The 25(OH) vitamin D level was determined as mean 16.3±8.4 ng/mL (range, 3-42) in the whole sample, with an insufficient level seen in 211(89.0%) patients. In the comparison of 25(OH) vitamin D levels between the groups, the 25(OH) vitamin D level was determined to be 16.8±8.5 in the group with Hp eradication and 12.7±6.5 in the group without Hp eradication. The difference between the two groups was found to be statistically significant (*p= 0.018*).

Conclusion: Before H pylori eradication treatment, it is important to maintain optimal levels of 25(OH) vitamin D, which has an effect on the effectiveness of eradication.

Keywords: Eradication, helicobacter pylori, 25(OH) vitamin D.

Özet

Amaç: H. pylori eradikasyonunda birçok faktörün rol oynadığı bilinmektedir. Bu çalışmanın amacı H. pylori'nin eradikasyon başarısına 25(OH) D vitamininin etkisini araştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Gastroenteroloji Polikliniğine en az 6 aydır devam eden dispeptik yakınmalarla başvuran 18-85 yaş arası 237 hasta dahil edildi. Hastalar 25(OH) vitamin D düzeyine göre >20ng/ml ve <20ng/ml olmak üzere iki gruptan ayrıldı. Hp eradikasyonu için hastalara gemifloksasin 320 mg 1x1 , amoksisilin 1 gr 2x1 ve rabeprazol 40 mg 1x1 tedavileri verildi. Tedaviden 1 ay sonra Hp'nin eradike edilip edilmediğinin tespiti için dışkı incelemesi yapıldı. D vitamini seviyesi yüksek ve düşük olan gruplar arasında eradikasyon oranları karşılaştırıldı.

Bulgular: Hastaların 139'u (%58,6) kadın, 98'i (%41,4) erkekti ve ortalama yaşları 40,9±14,1 (18-72 yaş arası) idi. D vitamini düzeyi ortalama 16,3±8,4 (3-42) olarak saptandı. 211 (%89,0) hastada yetersiz düzeyde görülmüştür. Gruplar arası D vitamini düzeyleri karşılaştırıldığında, Hp eradikasyonu yapılan grupta D vitamini düzeyi 16,8±8,5, Hp eradikasyonu yapılmayan grupta ise 12,7±6,5 olarak belirlendi.İki grup arasındaki fark istatistiki olarak anlamlı bulundu (*p=0,018*).

Sonuç: Hp eradikasyon tedavisi öncesinde, eradikasyonun etkinliğini etkileyen D vitamini düzeylerinin optimum düzeyde tutulması önemlidir.

Anahtar Sözcükler: D vitamini, eradikasyon, helikobakter pilori.

Introduction

Helicobacter pylori (Hp) is a microaerophilic gram-negative pathogen, which infects approximately half of the global population (1, 2). In the literature; diseases associated with Hp infection are gastritis, peptic ulcer, lymphoma and stomach cancer. (3).
In a previous study, it was determined that upper gastrointestinal bleeding due to peptic ulcer was less common in summer and autumn (4). In Hp eradication, the desired eradication rates cannot usually be reached due to both bacteria and host-related factors (5). Virulence factors affecting eradication; while the cytotoxin-related gene A product, vacuolating cytotoxin A, duodenal ulcer-promoting gene A product , external inflammatory protein A and blood group antigen-binding adhesion , the host factors are smoking, diet, treatment compliance, cytochrome P2C19 (CYP2C19) and interleukin-1 (IL-1) (6).
25(OH) vitamin D regulates calcium and phosphorus metabolism, which are essential for bone formation, and the effect of 25(OH) vitamin D on H. pylori infection and eradication rates has recently been widely studied(7,8). It is now increasingly recognized that VitD 3 is not only involved in diseases of the skeletal system, but also in many other physiological processes in the human body.(9)25(OH) vitamin D deficiency has been recognized as one of the potential risk factors for H. pylori treatment failure, and studies recommend adding 25(OH) vitamin D as an adjuvant to standard medications(10). Additionally, H. pylori positivity rates appear to be higher among populations with low serum 25(OH) vitamin D levels.(8,11)
The purpose of this study was to investigate the effect on the success of Hp eradication of 25(OH) vitamin D level, which was considered to be another factor, in a patient group where eradication was attempted with gemifloxacin, amoxicillin, and rabeprazole.

Material and Method

Study Design

This retrospective study included 237 patients, aged 18-85 years, who presented at the Gastroenterology Polyclinic between April 2021 and November 2021 with dyspeptic complaints which had been ongoing for at least 6 months. Informed consent was provided by all the patients. Study exclusion criteria include; chronic disease (liver, renal), organ transplantation(bone marrow, kidney, liver), had received antibiotic treatment within the last year, GİS surgery and pregnant.

Before starting the Hp eradication treatment, the serum 25(OH) vitamin D level was measured with the ELISA method. Patients were divided into two groups according to their 25(OH) vitamin D level as >20ng/ml and <20ng/ml. For Hp eradication, the patients were administered treatment of 1 x1 320mg gemifloxacin, 2 x 1 1gr amoxicillin, and 1 x1 40mg rabeprazole. After 1 month of treatment, faecal examination was made to determine whether or not Hp was eradicated. The eradication rates were compared between the groups with high and low level 25(OH) vitamin D.

Endoscopic evaluation

Endoscopic and histopathological findings of the patients were documented. Endoscopy was performed on all patients with the Fujinon EG530WR endoscopy device in our endoscopy unit.The endoscopy procedure was performed after an 8-hour fast and the application of local pharyngeal xylocaine anesthesia. The stomach and duodenum were detailed analysis during the endoscopy and biopsies were taken in respect of Hp infection.

Histopathological evaluation

During the endoscopy examination, biopsy was taken from the antrum by biopsy forceps. Paraffin blocks of the taken biopsy materails are cut to the suitable thickness and was painted with Giemsa. This preparations have was been examined by three different pathologists blinded to the clinical of patients.

25(OH) vitamin D measurement

Serum 25(OH) vitamin D concentration was measured by Abbott Architect I4000 SR immunoassay analyzer. The results of serum 25(OH) vitamin D measurements were expressed as ng/mL.

Ethical statement

Approval was obtained from the ethics committee of our hospital for this study. (Approval no:2022/23-01). Procedures were carried out in accordance with the Declaration of Helsinki and ethical standards. Written informed consent form was obtained from all participants.

Statistics

Data obtained in the study SPSS vn. 19.0 software. Data were expressed as mean ± standard deviation (SD) values, categorical data as numbers (n) and percentage (%). Parametric data were compared between groups with Student's t-test and Chi-square test was applied to categorical data. *($p<0.05$)* value was considered statistically significant.

Results

Endoscopically and histopathologically diagnosed and treated 237 patients with Hp infection were evaluated. The patients comprised 139 (58.6%) females and 98 (41.4%) males with a mean age of 40.9±14.1 years (range, 18-72 years). In the evaluations made after treatment, Hp eradication was obtained in 211 (89.0%) patients and not in 26

(11.0%). The 25(OH) vitamin D level was determined as mean 16.3±8.4 (range, 3-42) in the whole sample, with an insufficient level seen in 211(89.0%) patients. In the comparisons between the groups with and without Hp eradication, no significant difference was determined between the groups in respect of age, height, weight, smoking status, alcohol consumption, and comorbid diseases (*p>0.05*) (Table I). In the comparison of 25(OH) vitamin D levels between the groups, the 25(OH) vitamin D level was determined to be 16.8±8.5 in the group with Hp eradication and 12.7±6.5 in the group without Hp eradication. The difference between the groups was statistically significant (*p= 0.018*) 25(OH) vitamin D was seen to be at a sufficient level in 78 (37.0%) patients in the group with Hp eradication, and in 4 (15.4%) patients in the group where Hp eradication was not obtained, and the difference was statistically significant (*p=0.029*) (Table I).

Table I. Relationships between 25(OH) vitamin D level and Hp eradication

Variables	Patients with Hp eradication N:211 (89%)	Patients without Hp eradication N:26 (11%)	Total N:237	*P value*
Age (years)	41.1±13.6	39.3±18.2	40.9±14.1	*0.535*
Gender (female)	120 (56.9%)	19 (73.1%)	139 (58.6%)	*0.113*
Height (cm)	166.9±8.7	165.1±7.3	166.7±8.5	*0.291*
Weight (kg)	70.7±13.1	73.7±13.8	71.0±13.2	*0.276*
BMI	25.3±4.3	27.1±4.2	25.5±4.2	***0.043***
Smoking status				*0.316*
-smoker	61 (28.9%)	10 (38.5%)	71 (30.0%)	
-non-smoker	150 (71.1%)	16 (61.5%)	166 (70.0%)	
Alcohol consumption				
-yes	0 (0%)	0 (0%)	0 (0%)	-
-no	211 (100%)	26 (100%)	237 (100%)	
Comorbid disease				
-present	46 (21.8%)	7 (26.9%)	53 (22.4%)	*0.554*
-absent	165 (78.2%)	19 (73.1%)	184 (77.6%)	
25(OH) vitamin D level				***0.029***
-insufficient	133 (63.0%)	22 (84.6%)	211 (65.4%)	
-sufficient	78 (37.0%)	4 (15.4%)	26 (34.6%)	
25(OH) vitamin D level (mean±SD)	16.8±8.5	12.7±6.5	16.3±8.4	***0.018***

Discussion

In recent years, it has been observed that eradication of Hp has become more difficult due to the increase in antibiotic resistance. This condition is caused by both enviromental factors and host-related factors. The data obtained from this study showed that insufficient 25(OH) vitamin D level was a factor in failure of eradication of Hp(12).

Diverse different effects have been observed in previous studies of the effect of 25(OH) vitamin D. Guo et al. showed that the antimicrobial effect of 25(OH) vitamin D against Hp plays an important role in the homeostasis of gastric mucosa and in the protection of the host against Hp (13). In a rat model study by Zhang et al., intragastric administered 25(OH) vitamin D was shown to reduce Hp colonisation without changing serum calcium and phosphorus levels (14). Izquierdo et al. reported that in addition to the effect on bone metabolism, 25(OH) vitamin D could decrease inflammatory makers such as IL-6, CRP, IL-18,TNF-α, and increase the level of IL-10 (15). After artificial infection of the stomach with H. pylori in mice, oral administration of 25(OH) vitamin D3 has been shown to increase anti-Hp activity via VDR-Cathelicidin antimicrobial peptide (CAMP) as well as a significant reduction in colonization rates. (16,17)

In a study of 27,077 patients, Shafrir et al. observed that the 25(OH) vitamin D level was signficantly higher in the Hp-negative patient group. It was shown that for every 1ng/mL increase in serum 25(OH) vitamin D, the probability of Hp infection decreased by 1.5%. In addition, in our study, it was observed that the 25(OH) vitamin D level in patients with successful Hp eradication was significantly higher than in patients with unsuccessful Hp eradication (18). In the previous study, the effect of 25(OH) vitamin D level on both Hp colonization and Hp eradication was clearly shown. It was also similarly shown that the rate of successful Hp eradication was higher in the patient group with a high level of 25(OH) vitamin D. Similarly, in a metanalysis evaluating the impact of 25(OH) vitamin D levels on H. pylori infection, they concluded that low 25(OH) vitamin D levels may be responsible for the higher prevalence of H. pylori infection and may adversely affect bacterial eradication(19). Shahawy et al. showed that 25(OH) vitamin D supplementation to the classical triple therapy given for Hp treatment significantly increased the eradication rate(20).

The limitations of this study are the retrospective, single-centre design and the limited number of patients in the group without Hp eradication. The strength of the study is that it was done with a treatment regimen not previously used in the treatment of Hp.

Conclusion

Our study demonstrated that a high 25(OH) vitamin D level increased the success of Hp eradication. It is clear that the eradication of Hp has been made more difficult by antibiotic resistance and some other environmental factors. Therefore, it is important that before eradication treatment, 25(OH)vitamin D levels, which affect the efficacy of eradication, are kept at the optimum level. More prospective studies are needed to clarify the association of 25(OH) vitamin D replacement with Hp eradication and to evaluate its efficacy in treatment.

References

1. Hu Y, Zhu Y, Lu N-H. Recent progress in Helicobacter pylori treatment. Chinese Medical Journal. 2020;133(03):335-343.
2. Bener A, Uduman S, Ameen A, Alwash R, Pasha M, Usmani M, et al. Prevalence of Helicobacter pylori infection among low socio-economic workers. The Journal of Communicable Diseases. 2002;34(3):179-184.
3. Malfertheiner P, Link A, Selgrad M. Helicobacter pylori: perspectives and time trends. Nature reviews Gastroenterology & hepatology. 2014;11(10):628-638.
4. Zimmerman J, Arnon D, Beeri R, Keret D, Lysy J, Ligumski M, et al. Seasonal Fluctuations in Acute Upper Gastrointestinal Bleeding: Lack of Effect of Nonsteroidal Anti--inflammatory Drugs. American Journal of Gastroenterology (Springer Nature). 1992;87(11).
5. Uotani T, Miftahussurur M, Yamaoka Y. Effect of bacterial and host factors on Helicobacter pylori eradication therapy. Expert opinion on therapeutic targets. 2015;19(12):1637-1650.
6. de Brito BB, da Silva FAF, Soares AS, Pereira VA, Santos MLC, Sampaio MM, et al. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World journal of gastroenterology. 2019;25(37):5578.
7. Antico, Antonio, et al. "Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case–control study and review of the literature on the interaction of vitamin D with the immune system." Clinical reviews in allergy & immunology 42 (2012): 355-364.
8. Huang, Bin, et al. "Effect of 25-hydroxyvitamin D on Helicobacter pylori eradication in patients with type 2 diabetes." Wiener Klinische Wochenschrift 131 (2019): 75-80.
9. Zhang, Ye, et al. "Vitamin D3 eradicates Helicobacter pylori by inducing VDR-CAMP signaling." Frontiers in Microbiology 13 (2022): 1033201.
10. Shatla, Mokhtar M., Ahmed S. Faisal, and Mahmoud Z. El-Readi. "Is vitamin D deficiency a risk factor for Helicobacter pylori eradication failure?." Clinical Laboratory 2 (2021).
11. Assaad, Shafika, et al. "Dietary habits and Helicobacter pylori infection: a cross sectional study at a Lebanese hospital." BMC gastroenterology 18 (2018): 1-13.
12. Zhang, Mei. "High antibiotic resistance rate: A difficult issue for Helicobacter pylori eradication treatment." World journal of gastroenterology 21.48 (2015): 13432.
13. Guo L, Chen W, Zhu H, Chen Y, Wan X, Yang N, et al. H elicobacter pylori induces increased expression of the vitamin D receptor in immune responses. Helicobacter. 2014;19(1):37-47.
14. Zhou, Anni, et al. "Vitamin D3 inhibits helicobacter pylori infection by activating the VitD3/VDR-CAMP pathway in mice." Frontiers in Cellular and Infection Microbiology 10 (2020): 566730.
15. Izquierdo MJ, Cavia M, Muñiz P, de Francisco AL, Arias M, Santos J, et al. Paricalcitol reduces oxidative stress and inflammation in hemodialysis patients. BMC nephrology. 2012;13(1):1-7.
16. Hu, Wei, et al. "Vitamin D3 activates the autolysosomal degradation function against Helicobacter pylori through the PDIA3 receptor in gastric epithelial cells." Autophagy 15.4 (2019): 707-725.
17. Li, Mingxing, et al. "1, 25-Dihydroxyvitamin D3 suppresses gastric cancer cell growth through VDR-and mutant p53-mediated induction of p21." Life Sciences 179 (2017): 88-97.
18. Shafrir A, Shauly-Aharonov M, Katz LH, Paltiel O, Pickman Y, Ackerman Z. The association between serum vitamin D levels and Helicobacter pylori presence and eradication. Nutrients. 2021;13(1):278.
19. Yang, Liping, et al. "Effect of vitamin D on Helicobacter pylori infection and eradication: A meta-analysis." Helicobacter 24.5 (2019): e12655.
20. Shahawy, Mohamed S. EL, Zakarya M. Shady, and Abdullah Gaafar. "Influence of adding vitamin D3 to standard clarithromycin-based triple therapy on the eradication rates of Helicobacter pylori infection." Arab Journal of Gastroenterology 22.3 (2021): 209-214.

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Aksiyel Spondiloartritte C-Reaktif Protein/Albumin Oranının Hastalık Aktivitesi ile İlişkisi

The Relationship Between C-Reaktif Protein/Albumin Ratio and Disease Activity in Axial Spondyloarthritis

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Aksiyel Spondiloartritte C-Reaktif Protein/Albumin Oranının Hastalık Aktivitesi ile İlişkisi

Özet

Amaç: C-reaktif protein/albümin oranı (CAO) yakın zamanda yeni bir inflamatuar biyobelirteç olarak tanımlanmış ve inflamasyonun belirlenmesinde birçok hastalıkta potansiyel rolü ortaya konulmuştur. Bu çalışma, aksiyel spondiloartritte (axSpA) hastalık aktivitesinin belirlenmesinde CAO'nun rolünü araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışma retrospektif vaka-kontrol çalışmasıdır. Toplam 128 hasta ve 111 yaş-cinsiyet uyumlu sağlıklı kontrol çalışmaya dahil edilmiştir. Serum albumin, C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH) kaydedildi. CAO, serum CRP/Albumin şeklinde hesaplanmıştır. Hastalık aktivitesini belirlemek için Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI) ve Ankilozan Spondilit Hastalık Aktivite Skoru-CRP (ASDAS-CRP) skorları kullanıldı. Hastalar BASDAI skoruna göre iki alt gruba ayrıldı: ≥4 aktif hastalık, <4 inaktif hastalık olarak sınıflandı. Ayrıca axSpA hastaları radyografik ve non-radyografik hastalık olarak da alt gruba ayrıldı.

Bulgular: CAO, axSpA hastalarında sağlıklı kontrollerinden anlamlı şekilde daha yüksekti (Sırasıyla 1,42 (0,91-4,49) ve 0,46 (0,25-0,95), *p<0,001*). Aktif hastalığı olanlarda da inaktif hastalığa sahip olanlara göre CAO anlamlı derecede daha yüksek bulundu (sırasıyla 4,61 (2,04-6,87) ve 0,977 (0,75-1,52), *p<0,001*). CAO, CRP, ESH, BASDAI ve ASDAS-CRP ile anlamlı ölçüde korelasyon göstermekteydi (Sırasıyla *r=0,996, p<0,001; r=0,471, p<0,001; r=0,779, p<0,001, r=0,842, p<0,001*). CAO'nun aktif hastalığı inaktif hastalıktan ayırt etme gücü için eğri altında kalan alan (EAA) 0,795 (95% güven aralığı (CI) 0.714-0.861; *p<0.001*) idi.

Sonuç: CAO, axSpA'da hastalık aktivitesi ile iyi derecede korelasyon göstermektedir. AxSpA'nın tanı ve takibinde inflamasyonun potansiyel bir göstergesi olarak kullanılabilecek, yararlı bir biyobelirteç olabilir.

Anahtar Sözcükler: Aksiyal spondiloartrit, albumin, C-reaktif protein, C-reaktif protein/albumin oranı, inflamasyon.

Abstract

Objective: The C-reactive protein/albumin ratio (CAR) has recently emerged as a novel inflammatory biomarker, indicating its potential role in determining inflammation in various disorders. This study aims to investigate the role of CAO in determining disease activity in axial spondyloarthritis (axSpA).

Material and Method: This study is a retrospective case-control study. A total of 128 patients with axSpA and 111 age-gender-matched healthy controls were included in the study. Serum albumin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were recorded. CAR was calculated as serum CRP/Albumin. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) scores were used to determine disease activity. Patients were divided into two subgroups based on the BASDAI score: ≥4 was considered active disease, and <4 was considered an inactive disease. Additionally, axSpA patients were also subdivided into radiographic and non-radiographic disease groups.

Results: CAR was significantly higher in axSpA patients compared to healthy controls (1.42 (0.91-4.49) and 0.46 (0.25-0.95), *p<0.001*, respectively). Similarly, CAO was found to be significantly higher in patients with active disease compared to those with inactive disease (4.61 (2.04-6.87) and 0.977 (0.75-1.52), *p<0.001*, respectively). CAR showed a significant correlation with CRP, ESR, BASDAI, and ASDAS-CRP (*r=0.996, p<0.001; r=0.471, p<0.001; r=0.779, p<0.001, r=0.842, p<0.001*, respectively). The area under the curve (AUC) for distinguishing active from inactive disease using CAR was 0.795 (95% confidence interval (CI) 0.714-0.861; *p<0.001*).

Conclusion: CAR correlates highly with disease activity in axSpA. It can potentially be a useful biomarker for determining and monitoring inflammation in axSpA.

Keywords: Albumin, Axial Spondyloarthritis, C-reactive protein; C-reactive protein/albumin ratio, inflammation

Giriş

Aksiyel Spondiloartrit (axSpA), ağırlıklı olarak aksiyal iskeleti ve sakroiliak eklemleri etkileyen, ağrıya ve potansiyel olarak geri dönüşümsüz yapısal hasara yol açarak fonksiyonel kısıtlılık ile sonuçlanabilen kronik inflamatuar romatizmal bir hastalıktır (1). İnflamasyonun axSpA'nın patogenezinde ve gelişiminde rol oynadığı ve geç hastalık evresinde deformite ve sakatlığa katkıda bulunduğu bilinmektedir (2). Bu nedenle bu hastaların yönetiminde inflamasyon durumunu ve hastalık aktivitesinin izlenmesi uygun tedaviye olanak sağlar. Bu durum fonksiyonelliğin korunması ve kalıcı hasarların önlenmesi açısından oldukça önemlidir.

Eritrosit sedimantasyon hızı (ESH) ve C-reaktif protein (CRP) gibi akut faz reaktanları axSpA'nın hastalık aktivitesini değerlendirmede sıklıkla kullanılmaktadır (3,4). Ancak bu belirteçlerin klinik parametreler ve radyolojik bulgular arasında her zaman net bir korelasyonunun olmaması nedeniyle, axSpA'da hastalık aktivitesinin değerlendirilmesi güçlüğe neden olabilmektedirler (5). Bununla birlikte, hastalık aktif olsa bile hastaların yaklaşık üçte birinde seviyeleri normal sınırlar içinde olabilir; bu nedenle bu belirteçlerin seviyeleri inflamasyon durumu ile de mutlak korele olmayabilir (6). Bunun yanısıra ESH ve CRP romatizmal patolojiler dışında birçok enfeksiyonlar, obezite, metabolik sendrom gibi birçok durumda da yüksek saptanabilmektedir (7). İnflamasyonun değerlendirmesinde objektif yöntem olan manyetik rezonans (MR) görüntülemesinin ardışık ve rutin kullanımı ise günlük pratikte uygulanabilir bir izlem yöntemi değildir. Hastalık aktivitesinin değerlendirmesi için sıklıkla Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI) ve Ankilozan Spondilit Hastalık Aktivite Skoru (ASDAS) gibi kompozit indeksler kullanılmakta ancak bu indeksler içinde hasta değerlendirmesine dayalı birçok subjektif komponent içermektedir (8). Sonuç olarak axSpA'da tanısal ve prognostik biyobelirteçler açısından henüz karşılanmamış bir ihtiyaç söz konusu olduğundan inflamasyonun daha doğru şekilde belirlenmesi için arayış devam etmektedir.

Son yıllarda, CRP/albümin oranı (CAO), çeşitli kanserler, sepsis, romatizmal hastalıklar gibi birçok tıbbi durumlarda inflamasyonun yeni bir potansiyel göstergesi olarak ortaya çıkmıştır (9, 10, 11). CRP enfeksiyon ve inflamasyon gibi birçok durumda artan bir pozitif akut faz reaktanıdır. Negatif bir akut faz proteini olan albumin de sistemik inflamasyona yanıt olarak azalmaktadır (12). CAO, pozitif akut faz reaktanı CRP'nin, negatif akut faz reaktanı olan albumine entegre edilmesi ile elde edilir ve inflamatuar yanıtın şiddetine ilişkin yakın zamanda tanımlanmış nötrofil-lenfosit oranı (NLR) gibi yeni biyobelirteçlerden daha hassas olabileceği gösterilmiştir (13). CAO'nun pankreatik kanserde prognozla ilişkili olduğu ve NLR, trombosit-lenfosit oranı (PLR) ve prognostik indeks gibi diğer prognostik göstergelerden daha üstün olduğu gösterilmiştir (14).

AxSpA hastalarının değerlendirilmesinde inflamasyonu en doğru şekilde belirleyen basit ve hızlı biyobelirteçlere ihtiyaç vardır. CAO'nun birçok hastalıkta potansiyel prognostik ve tanısal bir araç olarak kullanımı artan ilgi ve araştırma alanıdır. AxSpA'da da inflamasyon göstergesi olarak kullanılabilirliğini değerlendiren çalışmalar mevcuttur (15-17). Zhong ve ark. CAO'nun AxSpA'da hastalık aktivitesini göstermede belirleyici bir faktör olabileceğini ileri sürmüşlerdir (15). Pamukçu ve ark. ise yaptıkları çalışmada CAO'nun hastalık aktivitesi ile anlamlı korelasyon gösterdiğini ve rutin poliklinik sırasında kullanılabilecek pratik bir değerlendirme aracı olduğunu değerlendirmişlerdir (16). Kaplan ve ark. ise CAO'nun AxSpA'nın yanısıra psöriatik artrit ve romatoid artritli hastalarda da hastalık aktivitesinin erken bir göstergesi olabileceğini vurgulamışlardır (17). Biz de çalışmamızda CAO'nun axSpA'da inflamasyon biyobelirteci olarak kullanılabilirliğini ve hastalık aktivitesi ile ilişkisini belirlemeyi ve sonuçları yukarıda bahsedilen çalışmalar ile karşılaştırmayı amaçladık. Çalışmamızda önceki çalışmalardan farklı olarak CAO'nun radyografik ve non-radyografik axSpA'lı hastalarda ve periferik tutuluma sahip olan axSpA'lı hastalarda farklılık gösterip göstermediğini de araştırmayı amaçladık.

Gereç ve Yöntemler

Bu retrospektif vaka-kontrol çalışması, Haziran 2020 ve Aralık 2020 tarihleri arasında ayaktan romatoloji polikliniğinde yürütülmüştür. Uluslararası SpondiloArtrit Derneği Değerlendirmesi (ASAS: The Assessment of SpondyloArthritis international Society) 2009 axSpA sınıflandırma kriterlerine (18) göre axSpA tanısı alan, 18 yaş üstünde 128 hasta ve yaş-cinsiyet uyumlu 111 sağlıklı kontrol çalışmaya dahil edildi. AxSpA hastaları non-radyografik (nr-axSpA) ve radyografik axSpA (r-axSpA) hastaları olmak üzere iki alt gruba ayrıldı. Gebelik, enfeksiyon, malignite, hipertansiyon, diyabet, ciddi kardiyovasküler hastalık, böbrek veya karaciğer bozuklukları, spot idrarda proteinüri, amiloidoz, ciddi kilo kaybı olanlar, axSpA dışında romatizmal veya otoimmün hastalığı olanlar çalışma dışı bırakıldı. Sağlıklı kontrol grubu, romatoloji polikliniğine başvuran ve yapılan muayene ve tetkik sonucunda romatizmal bir patoloji saptanmayan ve diğer çalışmaya dahil edilme ve dışlanma kriterlerine uyan sağlıklı bireylerden oluşmaktaydı. AxSpA, sağlıklı

grupta anamnez, fizik muayene ve gereklilik halinde görüntüleme ve laboratuvar değerlendirmelerine dayalı olarak dışlanmıştır.

Yaş, cinsiyet gibi demografik veriler ile hastalık süresi, insan lökosit antijeni-B27 (HLA-B27) pozitifliği, eşlik eden periferik artrit, üveit varlığı, kullanılan ilaçlar gibi klinik veriler hastane elektronik bilgi sisteminden taranarak kaydedilmiştir. Hastalık aktivitesini belirlemek için Bath Ankilozan Spondilit Hastalık Aktivite Indeksi (BASDAI: Bath Ankylosing Spondylitis Disease Activity Index) ve Ankilozan Spondilit Hastalığı Aktivite Skoru-CRP (ASDAS-CRP) skorları kullanıldı (16). Hastalar BASDAI değerlerine göre iki gruba ayrıldı; BASDAI≥4 olanlar aktif hastalık grubuna dahil edilirken, BASDAI<4 olanlar inaktif kabul edildi (19). AxSpA hastalarının yaşam kalitesi Ankilozan spondilit yaşam kalitesi ölçek puanı (ASQoL: Ankylosing Spondylitis Quality of Life) ile değerlendirildi. Sedimantasyon ölçümleri EDTA (BT-Lab) içeren tüplere alınan örneklerden Vision-b Sedimentation Cihazı (YHLO BIOTECH) ile elde edilmiştir. CRP ölçümleri ise immünoturbidimetrik teknikle Cobas Integra 800 (Roche Diagnostics Mannheim, GmbH) cihazı ölçülmüştür. Serum albumin düzeyleri ise biyokimya analizörü (Dimension RXL system, Siemens, Munich, Germany) ile analiz edilmiştir.

Çalışmanın birincil sonuç ölçütü olan CRP/albumin oranı, serum CRP değerlerinin, serum albumin değerlerine bölünmesi ile edilmiştir.

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İstatistik Yöntemler

Örneklem büyüklüğünün belirlenmesinde G-Power (G*power Ver.3,3,10, Franz Faul, Universitat Kiel, Germany) programı kullanıldı. Önder ve arkadaşlarının çalışması referans alınarak Tip I hata $\alpha=0,05$ ve %95 güç ve etki büyüklüğü 0.51 alındığında her bir gruba alınması gereken minimum örneklem sayısı 101 olarak belirlendi (20). İstatistiksel analizler IBM SPSS 23.0 (Statistical Package for the Social Sciences-23.0, Armonk, NY: IBM Corp) kullanılarak yapıldı. Değişkenlerin dağılımının normalliği Kolmogorov-Smirnov testi ile analiz edildi; değerlendirilen parametreler içinde sadece "yaş" normal dağılım gösterirken diğer parametreler normal dağılım göstermiyordu. Kategorik veriler sayı ve yüzde olarak verildi. Sürekli değişkenler ise normal dağılıma uyuyorsa ortalama ve standart sapma olarak, uymuyorsa median ve çeyrekler arası genişlik (Interquartile range-IQR) olarak verilmiştir. Labortauvar parametreleri, yaş, hastalık süresi, hastalık aktivite skorları gibi sürekli değişkenler normal dağılıyorsa, iki grup arasındaki (radyografik ve non-radyografik hastalar ile AxSpA ve kontrol grubu) farkı analiz etmek için Student t-testi, normal dağılım yoksa Mann-Whitney U testi kullanıldı. Katergorik değişkenlerin gruplar arası karşılaştırılması için ise Ki-Kare testi kullanıldı. 3 farklı grubun (kontrol gurubu, aktif ve inaktif hasta grubu) karşılaştırılmasında normal dağılım varsa tek yönlü varyans analizi (one-way ANOVA), yoksa Kruskal Wallis testi kullanıldı. CAO'nun laboratuvar parametreleri ve hastalık aktivitesi ile korelasyonunun değerlendirilmesinde değişkenler normal dağılım göstermediğinden Spearman korelasyon testi kullanıldı. Korelasyonlar; korelasyon katsayısı *<0,10*: ihmal edilebilir; *0,10-0,39*: zayıf; *0,40-0,69*: orta derece; 0,70-0,89: güçlü; 0,90-1,00: çok güçlü korelasyon olarak sınıflandırıldı. AxSpA hastalarını sağlıklı kontrollerden ayırt etme gücü için alıcı işletim özelliği (ROC-Receiver Operating Curve) analizi kullanıldı. $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya alınan 128 axSpA hastasının 93'ü (%72,7) erkek, 111 sağlıklı kontrolün 84'ü (%75,7)'si erkek, olup cinsiyetler arasında her iki grup arasında fark yoktu ($p=0,073$). AxSpA hastaları ile sağlıklı kontrol grubu arasında yaş ortalamaları arasında da fark saptanmadı (32,02±8,97 ve 34,40±11,11, $p=0,073$). Median (IQR) hastalık süresi 5 (4-8) yıldı. Toplam 128 AxSpA hastasının 43'ü (%33,6) nr-axSpA, 85'i (%66,4) r-axSpA olarak sınıflandırıldı. Hastaların 92'sinde (%71,9) HLA-B27 pozitif saptandı. AxSpA hastalarının 39'unda (%30,5) periferik artrit, 20'sinde üveit (%15,6) eşlik etmekteydi.

Median (IQR) CAO değerleri AxSpA hastalarında, sağlıklı kontrollerinden daha yüksekti (Sırasıyla 1,42 (0,91-4,49) ve 0,46 (0,25-0,95), $p<0,001$). Median ESH, CRP değerleri de sağlıklı kontrol grubuna göre istatistiksel olarak anlamlı yüksek saptandı (tümü için $p<0,001$). Albumin median düzeyleri ise axSpA grubunda sağlıklı kontrollerden daha düşük bulundu ($p<0,001$). Hastaların demografik, klinik ve laboratuvar özellikleri Tablo I'de özetlenmiştir.

Kontrol grubu, inaktif hastalık grubu ve aktif hastalık grubu arasında yapılan karşılaştırmada yaş ve cinsiyet açısından anlamlı farklılık saptanmazken, ESH, CRP, albümin ve CAO'da anlamlı farklılık tespit edildi. Sonrasında yapılan ikili karşılaştırmalarda kontrol grubu ile hem inaktif, hem de aktif hastalık grubu arasında anlamlı farklılık bulundu ($p<0.001$) (Tablo II). Aktif (BASDAI≥4) ve inaktif (BASDAI<4) AxSpA hastaları arasında yapılan ikili karşılaştırmada ise ESH, CRP ve CAO'nun median değerleri aktif

hastalığı olanlarda anlamlı derecede daha yüksekti (Sırasıyla *p<0,001, p<0,001 ve p<0,001*). Albumin median değeri ise aktif hastalıkta, inaktif hastalığa göre daha düşük bulundu (*p=0,02*).

Tablo I. AxSpA ve sağlık kontrollerin demografik, laboratuvar ve klinik özellikleri

	AxSpA (n = 128)	Sağlıklı kontrol (n = 111)	*p*
Yaş (yıl) (Ortalama+SS)	32.02 ± 8.97	34.40 ± 11.11	*0.073*
Cinsiyet [Kadın, n (%)]	35 (%27.3)	27 (%24.3)	*0.596*
Hastalık süresi (yıl)	5 (4-8)		
ESH (mm/s)	22 (16-31)	13 (7-21)	*<0.001*
CRP (mg/L)	5.65 (3.5-17.75)	2.1 (1.1-3.8)	*<0.001*
Albumin (g/dL)	4.1 (3.9-4.3)	4.4 (4.2-4.5)	*<0.001*
CAO	1.42 (0.91-4.49)	0.46 (0.25-0.95)	*<0.001*
BASDAI	3.10 (2.20-4.47)		
ASDAS-CRP	1.15 (1-2.4)		
ASQoL	3 (1-8)		
Non-radiografik axSpA	43 (33.6%)		
Eşlik eden periferik artrit, n (%)	39 (30.5%)		
HLA-B27 pozitifliğ, n (%)	92 (%71.9)		
Üveit Öyküsü, n (%)	20 (%15.6)		
Tedavi ajanı			
NSAİİ	33 (%25.8)		
Biyolojik Ajan	95 (%74.2)		

axSpA: Aksiyel spondiloartrit; SS: Standard Sapma ESH: Eritrosit sedimantasyon hızı; CRP: C-reaktif protein; CAO: CRP-albumin oranı; BASDAI: Bath Ankilozan Spondilit Hastalık aktivite İndeksi; ASDAS-CRP: Ankilozan Spondilit Hastalık aktivite skoru-CRP; ASQoL: Ankilozan Spondilit Yaşam Kalite Ölçeği Skoru; HLA: İnsan Lökosit Antijeni; TNF: Tümör Nekroz Faktörü; IL: İnterlökin. *p < 0,05* istatistiksel olarak anlamlı kabul edilmiştir

AxSpA hastalarının 85'i radyografik, 43'ü non-radyografik axSpA olmak üzere iki alt gruba ayrıldı. Median CAO düzeyleri açsından iki grup arasında anlamlı fark saptanmadı (Sırasıyla 1.53 (0.91-5.07) ve 1.3 (0.8-3.56), *p=0,439*). Her iki grup arasında yaş, cinsiyet, albumin, ESH ve CRP düzeyleri ile BASDAI ve AsQoL arasında da anlamlı fark yoktu (tümü için p>0,05) (Tablo III).

Periferik eklem tutulumu olan hastalarda median CAO düzeyleri olmayanlara göre daha yüksek bulundu (Sırasıyla 2,32 (1,14-4,63) ve 1,09 (0,76-3,57), *p=0,013*).

CAO median değerleri ise üveit öyküsü olan ve üveit öyküsü olmayan AxSpA'lı hastalar arasında ise anlamlı fark göstermemekteydi (*p=0,151*).

HLA-B27 pozitif ve negatif hastalar arasında da CAO değerleri arasında fark saptanmamıştır (*p=0,524*). CAO, albumin, CRP, ESH, BASDAI ve ASDAS-CRP ile de anlamlı ölçüde korelasyon göstermekteydi (Sırasıyla *r=-0,550, p<0,001; r=0,996, p<0,001; r=0,471, p<0,001; r=0,779, p<0,001, r=0,842, p<0,001*) (Tablo IV).

Tablo II. Kontrol grubu, inaktif hastalık grubu ve aktif hastalık grubunun karşılaştırılması

	Kontrol Grubu	İnaktif Hastalık BASDAI<4 (n = 71)	Aktif Hastalık BASDAI≥4 (n = 57)	*p*
Yaş (yıl) (Ortalama+SS)	34.4 ± 11.11	31.18 ± 8.88	33.11± 9.06	*0.170*
Cinsiyet, Kadın, n (%)	27 (%24.3)	18 (%25)	17 (%30.4)	*0.750*
Hastalık süresi (yıl)		5 (4-7.75)	5 (4-8)	*0.822*
ESH (mg/L)	13 (7-21)	17 (15-25)	28.5 (19.25-37.75)	*<0.001*
CRP (mg/L)	2.1 (1.1-3.8)	4 (3.05-5,975)	19 (8.64-27)	*<0.001*
Albumin (g/dL)	4.4 (4.2-4.5)	4.2 (4-4.3)	4 (3.8-4.2)	*<0.001*
CAO	0.46 (0.25-0.95)	0.977 (0.75-1.52)	4.61 (2.04-6.87)	*<0.001*
ASQoL		2 (1-3)	8 (4-11)	*<0.001*

BASDAI: Bath Ankilozan Spondilit Hastalık aktivite İndeksi, SS: Standard Sapma ESH: Eritrosit sedimantasyon hızı; CRP: C-reaktif protein; CAO: CRP-albumin oranı; ASQoL: Ankilozan Spondilit Yaşam Kalite Ölçeği Skoru. p < 0,05 istatistiksel olarak anlamlı kabul edilmiştir; İnaktif hastalık: BASDAI<4, Aktif hastalık: BASDAI≥4

CAO'nun aktif hastalığı inaktif hastalıktan ayırt etme gücü için yapılan ROC analizinde eğri altında kalan alan (EAA) 0,795 (95% güven aralığı (CI) 0.714-0.861; P<0.001) idi (Şekil I). CAO için optimal cut-off değeri 1,51 olup, duyarlılık %78,6, özgüllük %75 bulundu. CRP'nin aktif hastalığı inaktif hastalıktan ayırt etme gücü için EAA 0,791 (95% güven aralığı (CI) 0.710-0.857; P<0.001), duyarlılık %76,8, özgüllük %76,4, ESH için EAA 0,724 (95% güven aralığı (CI) 0.639-0.800; P<0.001) ve duyarlılık %62,5, özgüllük %63,9'du. CAO'nun axSpA'yı sağlıklı kontrollerden ayırt etme gücü için ise EAA 0,812 (95% CI: 0.758-0.866; P<0.001) idi. CAO için optimal cut-off değeri 0,90, duyarlılık %75,8, özgüllük %74,8 olarak bulundu. CRP için EAA 0,801 (95% güven aralığı (CI) 0.744-0.857; P<0.001), duyarlılık %74,2, özgüllük %73,9 ESH için EAA ise 0,745 (95% güven aralığı (CI) 0.683-0.808; P<0.001), duyarlılık %60,2, özgüllük %64,9 idi.

Tablo III. AxSpA alt gruplarının karşılaştırılması

	Radyografik axSpA (n =85)	Non-radyografik axSpA (n =43)	*p*
Yaş (yıl) (Ortalama+SS)	32.72 ± 8.91	30.65 ± 9.03	*0.223*
Cinsiyet, Kadın, n (%)	21 (%24.7)	14 (%32.6)	*0.348*
Hastalık süresi (yıl)	5 (5-7)	5 (3-9)	*0.435*
ESH (mg/L)	22 (16-31.5)	23 (15-31)	*0.834*
CRP (mg/L)	5.9 (3.65-19.5)	5.1 (3.3-11)	*0.510*
Albumin (g/dL)	4.1 (3.9-4.3)	4.2 (4-4.3)	*0.110*
CAR	1.53 (0.91-5.07)	1.3 (0.8-3.56)	*0.439*
BASDAI	3.4 (2.1-5.15)	3 (2.4-3.5)	*0.053*
ASDAS-CRP	1.2 (1-2.5)	1.1 (1-2.3)	*0.570*
ASQoL	3 (1-8)	3 (2-8)	*0.823*

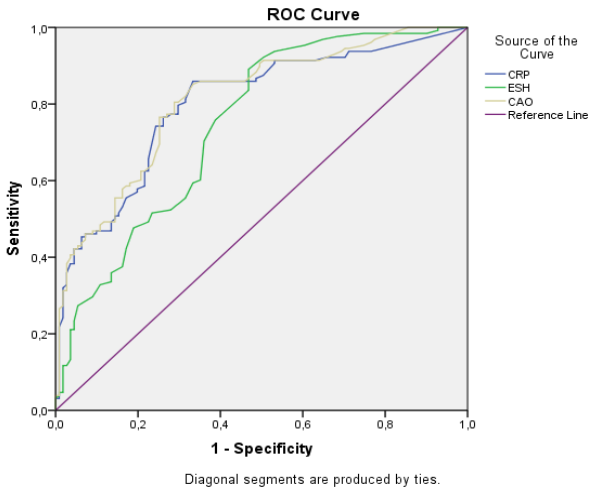
axSpA: Aksiyel spondiloartrit; SS: Standard Sapma ESH: Eritrosit sedimantasyon hızı; CRP: C-reaktif protein; CAO: CRP-albumin oranı; BASDAI: Bath Ankilozan Spondilit Hastalık aktivite İndeksi; ASDAS-CRP: Ankilozan Spondilit Hastalık aktivite skoru-CRP; ASQoL: Ankilozan Spondilit Yaşam Kalite Ölçeği Skoru. p < 0,05 istatistiksel olarak anlamlı kabul edilmiştir.

Tartışma

Bu çalışma axSpA'lı hastalarda CAO'nun hastalık aktivitesi ve hastalığın eklem dışı tutulumları gibi diğer klinik özellikleriyle olan ilişkisini belirlemek amacıyla yapılmıştır. CAO ile hastalık aktvitesi arasında da güçlü korelasyon bulunduğu belirlenmiştir. Ayrıca CAO'nun axSpA'yı sağlıklı kontollerden ayırt etme ve aktif hastalığı inaktif hastalıktan ayırt etme gücü için EAA, ESR ve CRP'den daha yüksek bulunmuştur. Ek olarak kontrol grubundaki hastalar ile karşılaştırıldığında, ESR, CRP değerleri ve CAO sadece aktif hastalık grubundan değil, inaktif hastalık grubunda da anlamlı ölçüde daha yüksekti. Son olarak CAO, periferik eklem tutulumu eşlik eden axSpA hastalarında da periferik eklem tutulumu eşlik etmeyenlere göre anlamlı derecede yüksek bulunmuştur.

Ax-SpA'da hastalık aktivitesinin değerlendirilmesi için BASDAI, ASDAS-CRP gibi skorlar yaygın olarak kullanılsa da bu belirteçlerin kısmi subjektif doğası nedeni ile standardize edilmiş, kolay uygulanabilir ve güvenilir belirteçlere ihtiyaç vardır (8). Artan kanıtlar nötrofillerin, trombositlerin, monositlerin ve lenfositlerin inflamasyonda rol oynadığını göstermektedir ve bu nedenle bu parametrelerin kombinasyonları, NLO, PLO ve monosit-lenfosit oranı (MLO), axSpA dahil olmak üzere birçok inflamatuar hastalıkta yeni inflamatuar göstergeler olarak ortaya çıkmıştır. Ancak literatürde bu belirteçlerin hastalık aktivasyonu ile korelasyonu arasında çelişkili sonuçlar mevcuttur. Örneğin; Bozan ve ark., (21) Enginar ve ark.'nın (22) aksine bu belirteçler ile hastalık aktivasyonu arasında korelasyon saptamamışlardır. Bu da axSpA'da daha sensitif biyobelirteçlerin halen araştırılmasına yol açmıştır. CAO, sistemik inflamasyon göstergesi olarak birçok hastalıkta araştırılmıştır (9, 13, 23). Çalışmamızda literatürle uyumlu olarak CAO ile ESH, CRP'nin yanısıra hem BASDAI hem de ASDAS-CRP ile değerlendirilen hastalık aktivasyonu arasında pozitif korelasyon olduğu gösterilmiştir (15,16,24). Ancak NLO, PLR gibi diğer inflamasyona dayalı belirteçlerle karşılaştırma yapılmamıştır.

Şekil I. AxSpA'lı hastalarda CAO, CRP ve ESH'nin aktif hastalığı inaktif hastalıktan ayırma gücü için yapılan ROC analizi sonuçları



CAO: CRP-albumin oranı; r: Rho katsayısı, CRP: C-reaktif protein; ESH: Eritrosit sedimantasyon hızı

Zhong ve ark.'nın (15) çalışmasında, bulgularımızla benzer şekilde CAO'nun axSpA hastalarında sağlıklı popülasyona göre anlamlı olarak arttığı, ESH, CRP, BASDAI ile güçlü bir şekilde ilişkili olduğu; ayrıca, aktif grupta inaktif gruba kıyasla anlamlı derecede daha yüksek olduğu tespit edilmiştir. Yine bu çalışmada, aktif gruptaki axSpA hastalarını inaktif gruptan ayırmada CAO'nun EAA'sının diğer biyobelirteçlerden (NLO, PLO, MLO, ESHve CRP) daha yüksek olup, Zhong ve ark. CAO'nun eğri altındaki alanını bize göre daha düşük bulmakla beraber (0,701 vs 0,795), bizimle benzer şekilde ESH ve CRP'den daha yüksek bulmuşlardır. Bu bulgular CAO'nun axSpA hastalarında inflamasyonun değerlendirilmesinde güvenilir bir biyobelirteç olduğunu düşündürmektedir. Bizim çalışmamızda da CRP, ESH ve CAO arasında en yüksek EAA CAO'da saptanmıştır. Benzer şekilde Pamukçu ve ark. (16) ve Slouma ve ark.'nın (24) çalışmalarında da CAO ile CRP, ESH ve hastalık aktivasyonu arasında pozitif korelasyon mevcuttur. Ayrıca Pamukçu ve ark. (16) ROC analizi

yapmamakla birlikte akut faz reaktanları normal olan hasta grubunda CAO ile BASDAI arasında orta düzeyde bir korelasyon olduğu gösterilmiştir. Kaplan ve ark. da (17) CAO'yu, aktif axSpA, psöriatik artrit ve romatoid artrit (RA) hastalığı olan hastalarda inaktif hastalığı olanlara göre anlamlı olarak daha yüksek bulmuşlar ve diğer inflamatuar indeksler ve akut faz reaktanları ile karşılaştırıldığında, CAO'nun, axSpA, ve RA hastalarında aktif hastalığın en önemli belirleyicisi olduğunu bildirmişlerdir.

Literatürde romatoid artrit, psöriasis, üveit, Takayasu arteriti ile ilgili çalışmalar da bu belirtecin hastalık aktivasyonu ile korelasyonunu desteklemektedir (11, 23,25-27). Yang ve ark. (23) ve Sunar ve ark.'nın (25) çalışmlarında romatoid artritte CAO ile ESH, CRP ve hastalık aktivite skoru-28 (DAS-28) arasında korelasyon olduğu gösterilmiştir. Seringec ve ark.'nın (11) çalışmasında Takayasu arteritli hastalarda ESH, CRP, CAO, NLO, PLO ve MLO kontrollere kıyasla anlamlı derecede yüksek, albümin ise anlamlı derecede düşük bulunmuştur. Aynı çalışmada CRP ve CAO düzeyleri hastalık aktivitesi ile pozitif korelasyon gösterirken, CAO Takayasu arteritinde hastalık aktivitesi ile en yüksek korelasyona sahip bulunmuştur.

CAO'nın üveit aktivasyonunun ve şiddetinin belirlenmesinde de önemli bir biyobelirteç olduğu bildirilmiştir. Bozkurt ve ark. (26) 35 üveiti olan hasta ve 35 sağlık kontrolünü değerlendirdikleri bu çalışmada CRP ve CAO'nın üveitli hastalarda anlamlı olarak daha yüksek bulunduğunu saptamışlardır. CAO hem anterior hem de posterior üveit için şiddetli üveiti olanlarda hafif derecede üveiti olanlara göre daha yüksek saptanırken, CRP düzeyleri için ise bu fark yanlızca anterior üveiti olanlarda saptanmıştır. Anterior üveit olan 15 hastanın yanlızca ikisi HLA-B27 ilişkili üveit olup, üveit etiyolojilerine göre ayrıca bir karşılaştırma yapılmamıştır. Kim ve ark. nın çalışmasında ise 50 Behçet üveiti, 52 HLA-B27 ilişkili üveiti olan hastalar dahil edilmiş olup her iki grupta da CAO üveit şiddeti ile ilişkili bulunmuş ve akut-kronik üveitin ayrımında sensitive bir biyobelirteç olabileceği belirtilmiştir (28). Bizim çalışmamızda üveit öyküsü olan ve olmayan hastalar arasında CAO değerleri arasında fark bulunmamıştır. Ancak ölçüm sırasında hiçbir hastada aktif üveit mevcut olmadığından üveit aktivasyonu sırasında CAO'nun axSpA'da üveit aktivasyonu ve şiddeti için inflamatuar bir biyobelirteç olarak kullanılabilirliği değerlendirilememiştir. Bu konu ile ilgili yapılacak çalışmalar CAO'nun HLA-B27 üveitinin aktivasyonunu öngörebilen bir biyobelirteç olarak kullanımı hakkında önemli bilgi kaynağı olacaktır.

AxSpA, AS olarak da adlandırılan radyografik ve non-radyografik hastalık formlarını içerir. Nr-axSpA'nın AS'in erken formu olabileceği gibi, ciddi ağrıyla seyreden ancak yapısal hasarla sonuçlanmayan hafif bir formu olabileceği de öne sürülmektedir. AS'li hastalarda hastalık aktivite düzeyleri ve ağrı şiddeti, yaşam kalitesi gibi hastalığın klinik yükü ise benzer olmakla beraber MR'da kemik iliği ödemi ve CRP düzeyleri gibi objektif inflamasyon bulguları nr-axSpA'dan daha fazla bulunmuştur (29). Bizim çalışmamızda hastalık aktivitesi ve yaşam kalitesi skorlarının yanısıra CAO ve ESH, CRP, albumin gibi inflamasyon belirteçleri açısından da radyografik ve non-radyografik grup arasında anlamlı fark saptanmamıştır. Ancak bu bulgu inflamatuar biyobelirteçler MR'da gösterilen inflamasyonla karşılaştırılmadığı ve çalışmaya sınırlı sayıda hasta dahil edildiği için genellenebilir bir sonuç olmayabilir.

AxSpA hastalarında periferik artrit varlığının daha yüksek hastalık aktivitesi (BASDAI) düzeyleri, daha düşük yaşam kalitesi ve daha fazla oranda steroid, konvansiyonel hastalık modifiye edici ve biyolojik ilaç kullanımı ile ilişkili olduğu bilinmektedir (30). Çalışmamızda diğer çalışmalardan farklı olarak periferik eklem tutulumu olan ve olmayan hastalarda CAO değerleri karşılaştırılmış olup periferik eklem tutulumu olan hastalarda median CAO düzeyleri olmayanlara göre daha yüksek bulunmuştur. Bu durum periferik artrit varlığında da takip ve tedavi etkinliğinin değerlendirilmesinde CAO'nun yararlı bir inflamatuar biyobelirteç olabileceğini düşündürmektedir.

Bu çalışmanın tek merkezli ve retrospektif dizayna sahip olması gibi bazı kısıtlılıkları mevcuttur. Ayrıca CAO'nun uzun süreli takip ve tedavi yanıtının değerlendirilmesindeki etkinliği değerlendirilememiştir. Yine MR'daki kemik iliği ödeminin varlığı ile CAO düzeyleri arasındaki ilişki de değerlendirilememiş olup, bu konuda yapılacak çalışmalar, CAO'nun inflamasyonu yansıtmadaki rolünü daha objektif bir şekilde ortaya koyabilir.

Sonuç

AxSpA'lı hastaların değerlendirilmesinde yaygın olarak kullanılan indeksler yoğun poliklinik ortamlarında zaman alıcıdır ve hasta tarafından değerlendirilen indeksler subjektif komponentler de içerdiğinden, olduğundan daha yüksek aktivite skoru değerleriyle sonuçlanabilir. Hastalık aktivasyonunun değerlendirilmesinde kullanılan CRP, ESH gibi biyobelirteçler aktif hastalıkta da normal aralıkta olabilir. Bu nedenle basit ve kolay uygulanabilen, hastalık aktivite indeksleriyle iyi derecede korelasyon gösteren ve hem pozitif hem de negatif akut fazı entegre eden CAO, ESH ve CRP'den daha güvenilir bir belirteç olabilir. CAO'nun takipte ve tedaviye yanıtın

değerlendirilmesinde, akut faz değerleri normal olan hastalarda güvenilirliğine yönelik daha çok çalışmaya ihtiyaç bulunmaktadır.

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Kaynaklar

1. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. BMJ 2006;333:581-585.
2. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 2019;7:22.
3. Ruof J, Stucki G. Validity aspects of erythrocyte sedimentation rate and C-reactive protein in ankylosing spondylitis: a literature review. J Rheumatol 1999;26:966-970.
4. Maksymowych WP. Biomarkers for Diagnosis of Axial Spondyloarthritis, Disease Activity, Prognosis, and Prediction of Response to Therapy. Front Immunol 2019;10:305.
5. Ozgocmen S, Godekmerdan A, Ozkurt-Zengin F. Acute-phase response, clinical measures and disease activity in ankylosing spondylitis. Joint Bone Spine 2007;74:249-253.
6. Rosa Neto NS, de Carvalho JF, Shoenfeld Y. Screening tests for inflammatory activity: applications in rheumatology. Mod Rheumatol 2009;19:469-477.
7. Kushner I, Rzewnicki D, Samols D. What does minor elevation of C-reactive protein signify?. Am J Med 2006;119:166.e17-166.e1.66E28.
8. Au YL, Wong WS, Mok MY, Chung HY, Chan E, Lau CS. Disease activity assessment in ankylosing spondylitis in a Chinese cohort: BASDAI or ASDAS?. Clin Rheumatol 2014;33:1127-1134.
9. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K. Clinical Significance of the C-Reactive Protein to Albumin Ratio for Survival After Surgery for Colorectal Cancer. Ann Surg Oncol 2016;23:900-907.
10. Kim MH, Ahn JY, Song JE, et al. The C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Patients with Severe Sepsis or Septic Shock Treated with Early Goal-Directed Therapy. PLoS One 2019;14:e0225620.
11. Seringec Akkececi N, Yildirim Cetin G, Gogebakan H, Acipayam C. The C-Reactive Protein/Albumin Ratio and Complete Blood Count Parameters as Indicators of Disease Activity in Patients with Takayasu Arteritis. Med Sci Monit 2019;25:1401-1409.
12. Grover HS, Saini R, Bhardwaj P, Bhardwaj A. Acute-phase reactants. J Oral Res Rev 2016;8:32-35.
13. Kalyoncuoglu M, Durmus G. Relationship between C-reactive protein-to-albumin ratio and the extent of coronary artery disease in patients with non-ST-elevated myocardial infarction. Coron Artery Dis 2020;31:130-136.
14. Arakawa Y, Miyazaki K, Yoshikawa M, et al. Value of the CRP-albumin ratio in patients with resectable pancreatic cancer. J Med Invest 2021;68:244-255.
15. Zhong Z, Huang Y, Liu Y, et al. Correlation between C-Reactive Protein to Albumin Ratio and Disease Activity in Patients with Axial Spondyloarthritis. Dis Markers 2021;2021:6642486.
16. Pamukcu M, Duran TI. Could C-Reactive Protein/Albumin Ratio be an Indicator of Activation in Axial Spondyloarthritis? J Coll Physicians Surg Pak 2021;30:537-541.
17. Kaplan H, Cengiz G, Şaş S, Eldemir YÖ. Is the C-reactive protein-to-albumin ratio the most remarkable simple inflammatory marker showing active disease in patients with axial spondyloarthritis, psoriatic arthritis, and rheumatoid arthritis? Clin Rheumatol 2023. doi: 10.1007/s10067-023-06703-8.
18. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-783.
19. M van der Heijde D, Sieper J, Maksymowych WP, et al. Assessment of SpondyloArthritis international Society. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:905-8.
20. Önder ENA, Cam FS, Ertan P. Relationship between C-reactive Protein/Albumin Ratio and Subclinical Inflammation in Patients with Familial Mediterranean Fever. Akt Rheumatol 2021;46:479–484.
21. Bozan N, Alpaycı M, Aslan M, et al. Mean platelet volume, red cell distribution width, platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in patients with ankylosing spondylitis and their relationships with high-frequency hearing thresholds. Eur Arch Otorhinolaryngol 2016;273:3663-3672.
22. Enginar AU, Kacar C. Neutrophil-lymphocyte and platelet-lymphocyte rate and their seasonal differences in ankylosing spondylitis and rheumatoid arthritis patients using anti-TNF medication. Bratisl Lek Listy 2019;120:586-592.
23. Yang WM, Zhang WH, Ying HQ, et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: Albumin to fibrinogen ratio and C-reactive protein to albumin

ratio. Int Immunopharmacol 2018;62:293-298.
24. Slouma M, Rahmouni S, Dhahri R, Gharsallah I, Metoui L, Louzir B. Neutrophil-to-lymphocyte Ratio, Platelet-to-lymphocyte Ratio, C-reactive Protein to Albumin Ratio, and Albumin to Fibrinogen Ratio in Axial Spondyloarthritis: A Monocentric Study. Curr Rheumatol Rev 2021;17:312-317.
25. Sunar İ, Ataman Ş. Serum C-reactive protein/albumin ratio in rheumatoid arthritis and its relationship with disease activity, physical function, and quality of life. Arch Rheumatol 2020; 35:247-253.
26. Bozkurt E, Muhafiz E, Sengul D, Uçak T, Atum M. Can the CRP/albumin Ratio be Used as a New Indicator of Activation in Patients with Uveitis? Ocul Immunol Inflamm 2021;29:1017-1022.
27. Tamer F, Avcı E. Serum C-reactive protein to albumin ratio as a novel inflammation biomarker in psoriasis patients treated with adalimumab, ustekinumab, infliximab, and secukinumab: a retrospective study. Croat Med J 2020;61:333-337.
28. Kim M, Park YG, Park YH. C-reactive protein/albumin ratio as an indicator of disease activity in Behçet's disease and human leukocyte antigen-B27-associated uveitis. Graefes Arch Clin Exp Ophthalmol 2021;259:1985-1992.
29. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences?. RMD Open 2015;1:e000053.
30. López-Medina C, Dougados M, Ruyssen-Witrand A, Moltó A. Evaluation of concomitant peripheral arthritis in patients with recent onset axial spondyloarthritis: 5-year results from the DESIR cohort. Arthritis Res Ther. 2019 Jun 6;21:139.

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Early and Mid-term Results of Endovascular Treatment of Abdominal Aortic Aneurysm in Patients Over 65 Years of Age

65 yaş Üstü Hastalarda Abdominal Aort Anevrizmasının Endovasküler Tedavisinin Erken ve Orta Dönem Sonuçları

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Early and Mid-term Results of Endovascular Treatment of Abdominal Aortic Aneurysm in Patients Over 65 Years of Age

Abstract

Objective: In patients over the age of 65, the most appropriate treatment modality for abdominal aortic aneurysms (AAA) is controversial, but the use of endovascular treatment methods is increasing. The aim of this study was to investigate the duration of intensive care unit stay, need for reintervention, and early and late mortality rates after endovascular treatment in octogenerians with abdominal aortic aneurysm.

Material and Method: A total of 220 patients who underwent endovascular aneurysm repair for abdominal aortic aneurysm under elective conditions were included in the study. Patients over 70 years of age constituted Group-1 (n=102) and those under 70 years of age constituted Group-2 (n=118). The groups were analyzed in terms of postoperative intensive care stay, need for reintervention, and early and late mortality rates.

Results: The ratio of males was higher in group 1 (94.5% vs. 84.9, *p=0.017*). Length of ICU stay was higher in group 1 (12 hours vs. 8 hours, *p=0.014*). All four cases of early mortality were in patients over 65 years of age (*p=0.031*). There was no difference between the groups in terms of follow-up period (32 vs. 31 months, *p=0.859*), late mortality (8% vs. 13%, *p=0.219*), or the need for secondary intervention (6% vs. 7%, *p=0.770*). There was no difference between the groups in terms of survival and the 3-year survival was 91% vs. 85%. (*p=0.199*).

Conclusion: In octogenerians, endovascular aneurysm repair can be performed with acceptable mortality rates and satisfactory mid-term outcomes.

Keywords: Abdominal, aortic aneurysm, endovascular repair.

Özet

Amaç: 65 yaş üstü hastalarda abdominal aorta anevrizmalarının en uygun tedavi yöntemi tartışmalıdır, ancak endovasküler tedavi yöntemlerinin kullanımı artmaktadır. Bu çalışmanın amacı, abdominal aorta anevrizması olan 65 yaş üstü hastalarda endovasküler tedavi sonrası yoğun bakım süresini, yeniden müdahale ihtiyacını ve erken ve geç dönem mortalite oranlarını araştırmaktır.

Gereç ve Yöntem: Elektif koşullar altında abdominal aorta anevrizması için endovasküler anevrizma onarımı uygulanan toplam 220 hasta çalışmaya dahil edildi. 65 yaşın üzerindeki hastalar Grup-1'i (n=102) oluştururken, 65 yaşın altındakiler Grup-2'yi (n=118) oluşturdu. Gruplar, postoperatif yoğun bakım süresi, yeniden müdahale ihtiyacı ve erken ve geç dönem mortalite oranları açısından analiz edildi.

Bulgular: Erkeklerin oranı grup 1'de daha yüksekti (94.5% vs. 84.9, *p=0.017*). Yoğun bakım süresi grup 1'de daha uzundu (12 saat vs. 8 saat, *p=0.014*). Erken mortalite gerçekleşen dört vakanın tümü 65 yaşın üzerindeki hastalardaydı (*p=0.031*). Gruplar arasında takip süresi (32 vs. 31 ay, *p=0.859*), geç dönem mortalite (8% vs. 13%, *p=0.219*) veya sekonder müdahale ihtiyacı (6% vs. 7%, *p=0.770*) açısından fark yoktu. Gruplar arasında yaşam süresi ve 3 yıllık yaşam oranı açısından fark yoktu, 3 yıllık yaşam oranı ise %91 vs. %85'ti (*p=0.199*).

Sonuç: Yaşlı hastalarda, endovasküler anevrizma onarımı kabul edilebilir mortalite oranlarıyla ve tatmin edici orta dönem sonuçlarıyla gerçekleştirilebilir.

Anahtar Sözcükler: Abdomial, aort anevrizması, endovasküler tamir.

Introduction

Abdominal aortic aneurysm (AAA) is an asymptomatic disease that is often detected incidentally and its frequency increase with age. In some cases, the first symptom may be aneurysm rupture.

AAA is currently treated with open surgical repair (OSR) and endovascular aneurysm repair (EVAR). The choice of these two treatment modalities is based on the patient's comorbid factors and the anatomical features of the aneurysm.

In older patients, the mortality and morbidity of OSR increases with the increase in comorbid factors. For this reason, EVAR has become the treatment of choice for AAA, especially in older patients, due to its minimally invasive nature and lower peri-operative complication rates (2). At the same time, the lower operative mortality and satisfactory early results of EVAR have led to an increase in its use in elderly patients and patients with comorbidities (3). Some studies have shown that EVAR has lower mortality and morbidity than surgical treatment in elective AAA patients with advanced age (4). While the technical success of EVAR in elderly patients is high, complication rates are also high (5).

The outcome of EVAR in patients over 65 years of age and those under 65 years of age is still a matter of debate.

In order to evaluate the safety and viability of EVAR in older patients, it is imperative to juxtapose the post-procedural outcomes of indiviuals within this age bracket against those under the age of 65. The aim of this study was to investigate the technical success, survival, and complication rates of EVAR in patients over 65 years of age.

Material and Method

This research was designed as a retrospective and observational study. A total of 220 patients who underwent EVAR under elective conditions for AAA between January 2015 and January 2020 were included in our study. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ankara Bilkent City Hospital Clinical Research Ethics Committee (No. E1-19-161, 24-12-2019).

Patients included in the study were divided into two groups as those under 65 years of age (n = 102) and over 65 years of age (n = 118). Both groups were analyzed in terms of follow-up periods, early mortality, late mortality, need for secondary intervention, length of intensive care unit stay, and discharge times.

All EVAR procedures were performed by a dedicated cardiovascular surgery team in a hybrid operating room setting. Ankura stent-graft systems (Lifetech Scientific Corporation, Shenzen,China) were employed to all patients The procedures were performed under general or local-regional anesthesia according to the preference of the surgical team, anesthesiologist, and patient. Modular endografts were placed using standard methods. After the procedure was completed, a final angiography was performed. Type 1 endoleaks were treated with balloon angioplasty and placement of an extension graft when necessary; type 2 endoleaks were monitored during follow-up.

Postoperative follow-up was performed clinically and radiologically at discharge, 1 month, 6 months, 12 months, and then annually. Computed tomography examination and Doppler ultrasonography were performed for the first time at postoperative one month. If there was no type 1 or 3 endoleak in the initial evaluation, subsequent endoleak and sac diameter evaluations were performed only with Doppler ultrasonography (1). Type 2 endoleaks were evaluated using Doppler ultrasonography only, because they are considered benign endoleaks in the absence of sac enlargement. If there was a suspicion of sac enlargement on ultrasonographic examination, this finding was evaluated using tomography. Sac enlargement was defined as an increase of at least 5 mm compared to the preoperative diameter. When a secondary intervention, such as extension of stent-graft was required was required, contrast-enhanced angiography was performed only in the hybrid room.

Statistical Analysis

The variables were analyzed using both visual methods, such as histograms and probability plots, as well as analytical methods, including the Kolmogorov–Smirnov/Shapiro–Wilk tests to assess the normality of data distribution. Continuous variables that were normally distributed were presented as mean ± standard deviation, while non-normally distributed variables were presented as median values with their range. Categorical variables were expressed as percentages and numbers. The Mann–Whitney U test and Chi-square test were used to compare demographic parameters, operating variables, and follow-up data. Kaplan–Meier analysis was performed to demonstrate long-term all-cause mortality. The log-rank test was conducted to assess difference between groups. A *p-value of* < 0.05 was deemed statistically significant, and statistical analysis was performed using SPSS for Windows version 15.0 software program (SPSS Inc., Chicago, IL, USA).

Results

Distribution and demographic characteristics of the patients are presented in Table-I. The second table provides information regarding the procedural

details od the patients. Among both groups there were more male patients than female, and this finding was statistically significant Group-1 (*p=0.028*). In addition, the duration of intensive care unit stay was significantly shorter in patients younger than 65 years (*p=0.004*). All four cases of mortality seen in the early period were in patients over 65 years of age (*p=0.038*).

Table I. Demographic datas

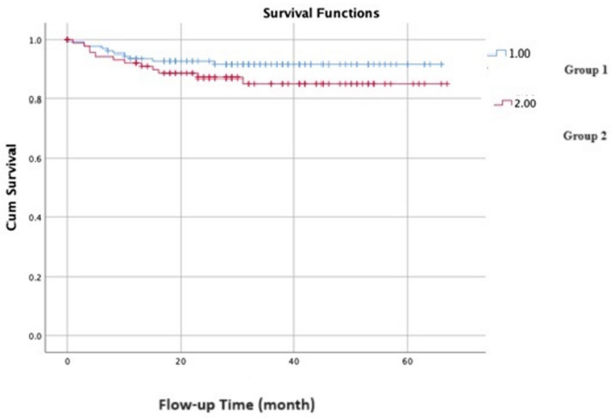
	Under 70 years old	Over 70 years old	*p value*
Age (year)	64.13±4.87	76.44±5.02	*< 0.001*
Gender (Male)	107 (94.7%)	92 (86.0%)	*0.028*
DM	30 26.5%	31 29.0%	*0.688*
HT	76 67.3%	78 72.9%	*0.362*
HL	34 30.1%	31 29.0%	*0.856*
COPD	25 22.1%	33 30.8%	*0.142*
PVD	11 9.7%	8 7.5%	*0.551*
CAD	39 34.5%	47 43.9%	*0.153*
CHF	3 2.7%	6 5.6%	*0.322*
Smoking	56 49.6%	53 49.5	*0.997*
TIA/CVE	5 4.4%	10 9.3%	*0.148*
Cancer	3 2.7%	3 2.8%	*1.000*
Symptom	37 32.7%	28 26.2%	*0.285*
EF (%)	52.88± 8.45	52.22± 9.10	*0.410*
Aneurysm Diameter(mm)	64.17± 14.01	66.27± 13.79	*0.127*
Procedure Duration (min)	146.78±43.36	142.79±56.53	*0.203*
Scopy Duration (min)	17.29± 12.02	17.63± 12.26	*0.827*
Opaque Quantity (cc)	64.10± 23.90	61.24± 25.19	*0.676*
IC Duration (hour)	8.20±24.28	11.40±19.22	*0.004*
Discharge Time (day)	2.58±2.38	2.74±2.44	*0.643*
Early Mortality	0 0.0%	4 3.7%	*0.038*
Follow-up (month)	33.85±16.94	35.32±16.94	*0.647*
Last pouch diameter (mm)	62.62±17.36	65.58±17.03	*0.312*
Late Mortality	10 8.8%	13 12.1%	*0.437*
Secondary Initiative	7 6.2%	8 7.5%	*0.719*

DM: Diabetes Mellitus **HT:** Arterial Hypertension **HL:** Hyperlipidemia
COPD: Chronic Obstrutive Pulmonary Diease **PVD:** Peripheral Vascular Disease
CAD: Coronary Artery Disease **TIA/CVE:** Transial İschemic Attack/Cerebrovascular Event
EF: Ejection Fraction

There was no significant difference between the two groups in terms of comorbid characteristics (diabetes mellitus, chronic obstructive pulmonary disease, hypertension, coronary artery disease, and peripheral artery disease).

No significant difference was found in terms of follow-up time (32 vs. 31 months, *p=0.859*)
There was no difference in late mortality (8% vs. 13%, *p=0.219*) and the need for secondary intervention (6% vs. 7%, *p=0.770*).

Figure I. Kaplan Meier Analysis of patients



In the last 5 years, a total of 220 EVAR patients were included in the study:

- Male gender predominates in patients under 70 years old compared to females (94.5% vs. 84.9%, *p=0.017*).
- Length of stay in the intensive care unit was longer for patients over 70 years old (12 hours vs. 8 hours, *p=0.014*).
- All 4 cases of early mortality occurred in patients over 70 years old (*p=0.031*).
- There was no significant difference in terms of follow-up duration for the patients (32 vs. 31 months, *p=0.859*).
- There was no statistically significant difference between the groups in terms of late mortality (8% vs. 13%, *p=0.219*) and secondary intervention rates (6% vs. 7%, *p=0.770*).

No difference was found between the two groups in terms of survival, and the 3-year survival was 91% vs. 85% (log-rank *p=0.199*) (Figure-I).

There was no difference in aneurysm diameters between the two groups (*p=0.127*).

Discussion

In patients with AAA of an advanced age with comorbidities, the treatment management and treatment process can be challenging. The aim of elective repair in patients with AAA is to prevent rupture, which can often be fatal.

In older patients, EVAR can be performed with acceptable mortality rates as we have shown in our study. At the same time, the mid-term survival rates of older patients after EVAR are satisfactory when compared with younger patients, which is demonstrated by our findings.

Current guidelines do not provide clear data on

the application of EVAR in elderly patients, and do not recommend EVAR only in patients with a life expectancy of two or three years (6).

In a surveillance study conducted in patients who were ineligible for AAA repair, it was shown that the risk of rupture increased in direct proportion with the diameter of the AAA annually (7). Therefore, prevention of rupture, which is the most deadly complication of AAA, should be considered the most important issue without question.

Endovascular treatment of AAA was introduced in 1990 and is becoming the main treatment option especially in patients with high comorbidity who are not suitable for surgical treatment (8). In various randomized controlled trials, patients who were anatomically suitable for EVAR and OSR, patients were compared in terms of early mortality and mid-term outcomes and similar results were obtained for EVAR and OSR (9).

In a 2016 study, it was shown that endovascular treatment of AAA was superior to OSR in terms of early survival but not in terms of late survival (10). In the same study, it was also shown that patients who underwent EVAR needed more re-interventions during long-term follow-up.

One of the main factors affecting the success of endovascular treatment is the patient having appropriate anatomical structure. Some studies have shown that in older patients, anatomical difficulties may negatively affect the results of endovascular treatment (11).

In the present study, the need for re-intervention was found to be low in patients of an advanced age who underwent EVAR, and there was no difference in mortality between the groups in the mid-term follow-up. Mortality occurred in four patients in the early period and all of these patients were over 65 years of age. The causes of these deaths were myocardial infarction in three patients and mesenteric ischemia in one patient. Myocardial infarction and cardiac complications may occur after EVAR and early troponin monitoring is recommended to recognize these conditions in the early period (12). Early troponin elevation after EVAR is considered a risk factor for early mortality. In the present study, two patients who died due to myocardial infarction also had elevated troponin levels measured on admission to the intensive care unit after the procedure.

No significant difference was found between the groups in terms of aneurysm diameter. Aneurysm diameter is the most important factor determining the risk of rupture. It was found that the risk of death and rupture was 11% when the diameter of the aneurysm was 5.1–6 cm, and this rate increased to 20% when the diameter was between 6.1–7 cm, and to 43% when the diameter was above 7 cm (7-13). The prevalence of AAA in the population over the age of 65 is approximately 1.5% (14). In a study conducted in a population aged 65–74 years, the incidence of mortality due to AAA was 36/100,000 people in the early 2000s, and this rate decreased to 10/100,000 people in 2015 (15). In this study, the reason for the decline in AAA-related mortality was stated as the increased frequency of screening, especially in the population over 65 years of age, and elective surgery before AAA rupture.

Complication rates for both OSR and EVAR are undoubtedly higher in the population over 65 years of age. In patients in this age group, the duration of hospitalization, intensive care unit stay, and need for blood transfusion were higher after OSR, whereas these rates were found to be lower in patients in the same age group who underwent EVAR (16).

Current guidelines do not provide clear recommendations for reducing age-related complications after EVAR (5). The results obtained in the present study showed that the early and mid-term outcomes for patients over 65 years of age who underwent EVAR were similar to those of younger patients and were acceptable. Management of patients with advanced age and minimization of procedural complications contribute to the survival of patients in this age group, as we have shown in the present study.

The most important limitation of the present study is that it was single-center study and retrospective in nature. Another limitation was that only patients treated with the endovascular method were included and patients who underwent surgical treatment were not analyzed. Hence, a comparison between EVAR and open surgical treatment could not be conducted.

Conclusion

With increasing technical experience in endovascular treatments, EVAR can be performed in patients over 65 years of age with additional comorbidities with satisfactory early and mid-term results.

References

1- Iscan HZ, Unal EU, Akkaya B et al. Color Doppler ultrasound for surveillance following EVAR as the primary tool.J Card Surg 2021;36:111-117.
2- Lagergren E, Chihade D, Zhan H et al. Outcomes and Durability of Endovascular Aneurysm Repair in Octogenarians. Ann Vasc Surg 2019;54:33-39.
3- Park BD, Azefor NM, Huang CC, Ricotta JJ. Elective endovascular aneurysm repair in the elderly: trends and outcomes from the Nationwide Inpatient Sample.

Ann Vasc Surg 2014;28:798-807.
4- Biancari F, Catania A, D'Andrea V. Elective endovascular vs. open repair for abdominal aortic aneurysm in patients aged 80 years and older: systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2011;42:571e6.
5- Rueda-Ochoa OL, van Bakel P, Hoeks SE et al. Survival After Uncomplicated EVAR in Octogenarians is Similar to the General Population of Octogenarians Without an Abdominal Aortic Aneurysm. Eur J Vasc Endovasc Surg 2020;59:740-747.
6- Wanhainen A, Verzini F, Van Herzeele et al.Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms.Eur J Vasc Endovasc Surg 2019;57:8-93.
7- Western CE, Carlisle J, McCarthy RJ, Currie IC. Palliation of abdominal aortic aneurysms in the endovascular era. Eur J Vasc Endovasc Surg 2013;45:37e43.
8- Han Y, Zhang S, Zhang J, Ji C, Eckstein HH. Outcomes of Endovascular Abdominal Aortic Aneuyrsm Repair in Octogenarians: Meta-analysis and Systematic Review. Eur J Vasc Endovasc Surg 2017;54:454-463.
9- Geisbüsch P, Katzen BT, Tsoukas AI et al. Endovascular repair of infrarenal aortic aneuyrsm in octogenarians and nonoctogenarians. J Vasc Surg 2011;54:1605-1613.
10- Patel R, Sweeting MJ, Powell JT, Greenhalgh RM; EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomized controlled trial. Lancet 2016;388(10058):2366-2374.
11- Pol RA, Zeebregts CJ, van Sterkenburg SM, Ferreira LM, et al. Outcome and quality of life after endovascular abdominal aortic aneurysm repair in octogenar- ians. J Vasc Surg 2014;60:308e17.
12- P J Devereaux, Bruce M Biccard, Alben Sigamani et al, Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2017;317:1642-1651.
13- VaitėnasG, Mosenko V, Račytė A, Medelis K, Skrebūnas A. Baltrūnas Abdominal Aortic Aneurysm Diameter versus Volume: A Systematic Review. T.Biomedicines 2023;11:941.
14- Wanhainen A, Hultgren R, Linné A, et al. Outcome of the Swedish nationwide abdominal aortic aneurysm screening program. Circulation 2016;134:1141e8.
15- Johansson M, Zahl PH, Siersma V, Jørgensen KJ, Marklund B, Brodersen J. Benefits and harms of screening men for abdominal aortic aneurysm in Sweden: a registry-based cohort study. Lancet 2018;391:2441e7.
16- Fonseca R, Rockman C, Pitti A, et al. Intermediate-term EVAR outcomes in octogenarians. J Vasc Surg 2010;52:556e60.

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The Relationship Between Serum Growth Differentiation Factor-15 Levels and Clinical Outcomes in Infertile Women Receiving In-vitro Fertilization Treatment

İn-vitro Fertilizasyon Tedavisi Alan İnfertil Kadınlarda Serum Büyüme Farklılaşma Faktörü-15 Düzeyi ile Klinik Sonuçlar Arası İlişki

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The Relationship Between Serum Growth Differentiation Factor-15 Levels and Clinical Outcomes in Infertile Women Receiving In-vitro Fertilization Treatment

Abstract

Objective: It has been reported in many studies that Growth Differentiation Factor-15 (GDF-15) has an important role in physiological or pathological processes. This study was aimed to investigate the role of GDF-15 in infertility and its treatment outcomes.

Material and Method: According to their ovarian reserve characteristics, 88 infertile women were divided into three groups: normal ovarian reserve (NOR) (n= 42), diminished ovarian reserve (DOR) (n= 22), and polycystic ovary syndrome (PCOS) (n= 24). Serum estradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Mullerian hormone (AMH), and GDF-15 levels were measured in their serum. The antagonist protocol patients' total oocyte, meiosis II (MII) oocytes, embryo count, and clinical pregnancy rates were documented and compared.

Results: In terms of serum GDF-15 concentrations, there was no statistically significant difference among the mean values of the three study groups. The mean FSH level at baseline was substantially higher in the DOR group compared to the PCOS group *(p=0.006*)*. The median serum AMH levels of all three groups were found to be statistically different *(p=<0.001*)*. When the groups were compared in terms of averages of total oocytes, MII oocytes, and embryos, it was observed that the NOR group and the PCOS group both had higher values than the AOR group *(p=0.001*)*.

Conclusion: In our study, a significant and strong relationship was found between serum GDF-15 level and the number of embryos formed as a result of in-vitro fertilization (IVF) treatment. Thereby, serum GDF-15 level may be considered to be a biomarker for predicting IVF clinical outcomes.

Keywords: GDF-15, growth Differentiation Factor- 15, IVF, infertility, ovarian reserve

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Özet

Amaç: Büyüme Farklılaşma Faktörü-15 (GDF-15)'in fizyolojik veya patolojik süreçlerde önemli rolu olduğu birçok çalışmada bildirilmiştir. Bu çalışmada GDF-15'in infertilitedeki rolünün ve tedavi sonuçlarının araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya 88 infertil kadın dahil edildi ve over rezerv özelliklerine göre çalışma populasyonu üç gruba ayrıldı. Bunlar; normal over rezervi (NOR) grubu (n= 42), azalmış over rezervi (AOR) grubu (n= 22), polikistik over sendromu (PKOS) grubu (n= 24). Serumlarında östradiol (E2), follikül uyarıcı hormon (FSH) ve luteinize edici hormon (LH), anti-müllerian hormon (AMH) ve GDF-15 düzeyleri ölçülmüştür. Antagonist protokolü ile tedaviye alınan hastaların total oosit, mayoz II (MII) oosit, embriyo sayısı ve klinik gebelik oranları dökümente edilmiştir.

Bulgular: Serum GDF-15 konsantrasyonları dikkate alındığında her üç çalışma grubunun ortalama değerleri arasında istatistiksel yönden anlamlı bir fark bulunmamıştır. Bazal FSH ortalaması AOR grubunda PKOS grubundaki katılımcılara göre anlamlı düzeyde yüksekti *(p=0,006*)*. Her üç grubun serum AMH düzey ortancası istatistiksel anlamlılıkta farklı bulunmuştur*(p=<0,001*)*. Total Oosit, MII oosit ve embriyo ortalama karşılaştırmalarında NOR grubu AOR grubuna göre *(p=<0,001*)* ve PKOS grubu AOR grubuna göre (p=<0,001*) daha yüksek değerlere sahiptir. Gruplar total oosit, MII oosit ve embriyo ortalamaları bakımından karşılaştırıldığında NOR grubu AOR grubuna göre *(p=<0,001*)*, PKOS grubu da AOR grubuna göre (p=<0,001*) daha yüksek değerlere sahip olduğu görüldü.

Sonuç: Çalışmamızda serum GDF-15 düzeyinin in-vitro fertilizasyon (İVF) tedavisi sonucunda oluşan embriyo sayıları arasında anlamlı ve güçlü bir ilişki saptanmıştır. Dolayısı ile serum GDF-15 düzeyi İVF klinik sonuçlarını öngören bir biyobelirteç olabileceği düşünülebilir.

Anahtar Sözcükler: Büyüme farklılaşma faktörü-15, GDF-15, İVF, infertilite, over rezervi

Introduction

The term ovarian reserve generally refers to a woman's reproductive capacity, specifically associated with the quantity and quality of her oocytes. Ovarian reserve is a complex clinical condition that is influenced by age, genetics, and environmental factors (1). Identifying infertile women at risk of diminished ovarian reserve (DOR) is one of the purposes of using ovarian reserve tests in clinical practice. It is also known that patients with DOR respond significantly less effectively to ovulation induction and in-vitro fertilization (IVF) treatments. It is also aimed at determining the probability of the development of ovarian hyperstimulation syndrome before treatment. By assessing ovarian reserve comprehensively and precisely, it aims to reduce the number of unnecessary treatments given to patients who are incorrectly classified as DOR but have normal ovarian reserve (NOR) (2).

Ovarian reserve tests applied to patients in clinical applications are performed with both biochemical tests and ultrasonographic imaging. The measurement of serum anti-Mullerian hormone (AMH) level and the count of total antral follicles count (AFC) in the extant ovaries are the most generally preferred and most reliable ovarian reserve tests. It has been determined in many studies that both tests are of equivalent value (3). Neither AMH nor AFC correlate strongly with qualitative outcomes such as oocyte quality, clinical pregnancy rate, or live birth rate (4). Bootcov et al. achieved the first cloning of Growth Differentiation Factor-15 (GDF-15) from a human monocytic cell line in 1997. GDF-15 is also an autocrine protein that modulates lipopolysaccharide-activated macrophages by inhibiting the production of tumour necrosis factor (TNF).Consequently, its initial name was GDF-15 Macrophage Inhibitory Cytokine-1 (MIC-1) (5). Due to the diversity of biological functions in both physiological and pathological processes, GDF-15 has been referred to by numerous other names in subsequent studies (including Nonsteroidal Anti-Inflammatory Drug Activated Gene-1, Placental Transformation Growth Factor, Prostate-Derived Factor, and Placental Bone Morphogenic Protein (6). GDF-15 Transforming Growth Factor (TGF) is a member of the superfamily that exhibits significant functional distinctions from its other members (7). In general, GDF-15 functions as a hormone, a cytokine induced by stress, or a stress-sensitive blood factor (8). The expression of GDF-15 was mostly detected in the placenta and prostate of healthy individuals (9). GDF-15 is also expressed at low levels in the mammary glands, kidney, liver, lung, colon, pancreas, endometrium, and peripheral and central nervous systems (10).

According to studies in the known literature, GDF-15 cardiovascular diseases (heart failure, acute coronary syndrome), kidney diseases (acute kidney disease, diabetic nephropathy, IgA nephropathy, amyloidosis, idiopathic membranous nephropathy), liver diseases (non-alcoholic fatty liver disease, liver cirrhosis, hepatitis C infection), metabolic syndrome, diabetes mellitus, sepsis, and iron metabolism-related anemia are known to be significantly associated with many medical conditions (11). Despite the fact that the functions of GDF-15 in a variety of physiological or pathological processes have been reported, there is currently no research on infertility and GDF-15 treatments.

Therefore, the purpose of this study was to investigate the potential relationship between GDF-15 and treatment outcomes in infertile women undergoing IVF treatment based on their ovarian reserve type.

Material and Method

Study population and design

This prospective observational study was conducted at the Hitit University Faculty of Medicine IVF Centre between January 1, 2022, and March 31, 2023. The Hitit University Ethics Committee approved this study, and it complies with the Declaration of Helsinki (Decision No. 493 dated October 13, 2021).

All participants were informed, and consent was obtained prior to the study. All participants' medical characteristics relevant to the study were recorded during the initial interview. The exclusion criteria of the study were the presence of previous pelvic surgery, endometriosis, adnexal mass, chemotherapy, radiotherapy, smoking, systemic diseases that may affect fertility potential, and drug use.

The body mass index (BMI) was calculated as weight (kg/height (m2)) using the height and weight measurements obtained during the initial physical examination. Pelvic evaluation and AFC were performed using an ultrasonography device with a transvaginal 7.5 MHz probe (Toshiba Xario 100, Toshiba Medical System Co., Nasu, Japan) during the early proliferative phases of the participants' menstrual cycles.

"Unexplained infertility" is defined as the absence of an identifiable cause of infertility after at least 12 months of trying to get pregnant in an evaluation (12). The most widely accepted criteria for the diagnosis of "polycystic ovary syndrome (PCOS)" are the Rotterdam Criteria, prepared by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (13). According to the Rotterdam Criteria, the diagnosis

of PCOS requires the presence of at least two of the following features:
1- Anovulation or oligoovulation
2- The presence of clinical and/or biochemical indicators of hyperandrogenism
3- Ultrasonography demonstrates polycystic ovary morphology [12 or more follicles 2-9 mm in diameter per ovary and/or increased ovarian volume (over 10 ml)]
The diagnosis of DOR is established using the Bologna criteria (14). According to these requirements, the definition of DOR must include at least two of the following:
1- Maternal age is advanced (>40 years)
2- Obtaining fewer than three oocytes following standard ovarian stimulation
3- Abnormal ovarian reserve tests (AFC < 5-7 and/or AMH level < 1.1 ng/ml)
Consequently, 88 infertile female participants who were scheduled to undergo IVF treatment and who met the inclusion criteria were accepted for participation in the study. The study population was classified into three study groups according to the ovarian reserve characteristics defined above.
(i) NOR group (infertile women diagnosed with unexplained infertility, n= 42)
(ii) DOR group (infertile women diagnosed with DOR, n = 22)
(iii) PCOS group (infertile women diagnosed with PCOS, n = 24)

Sample collection and measurements

Venous blood samples were taken from all participants between 9:00 and 10:00 in the morning after an 8–10 hour fasting night on days 2-4 of the menstrual cycle. Blood samples were centrifuged at 1000 x g for 20 minutes for hormonal analysis. The serum concentrations of estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured daily using an autoanalyzer (Cobas 6000, E601, Roche Diagnostics GmbH, Mannheim, Germany) and the electrochemiluminescence immunoassay (ECLIA) technique. After centrifugation, blood samples were frozen at -80 °C for measurements of AMH and GDF-15. AMH levels were measured using ECLIA on an autoanalyzer (Cobas 6000, E601, Roche Diagnostics GmbH, Mannheim, Germany), whereas GDF-15 levels were measured using ELISA (Bioassay Technology Laboratory, Shanghai, China).

Ovarian stimulation and oocyte retrieval

Controlled ovarian stimulation (COS) of infertile women undergoing IVF with the antagonist protocol started with subcutaneous injections of recombinant FSH (Gonal-F, Merck Serono, S.p.A., Modugno, Italy) in individualized doses (150-300 IU daily) on days 2 or 3 of the menstrual cycle. During the treatment's follow-up, transvaginal ultrasonography and serum E2 levels were both used to monitor follicle development. When at least one of the responding follicles reached a diameter of 13 mm, daily subcutaneous injections of 250 mcg cetrorelix (Cetrotide, Merck, Pierre Fabre Medicament Production, Idron, France) were given. Ovulation was triggered by a single subcutaneous injection of 250 mcg of recombinant human choriogonadotropin (rhCG) (Ovitrelle, Merck Serono, S.p.A., Modugno, Italy) when at least three follicles measuring 18 mm in diameter were obtained as a result of COS. After 34 to 36 hours of ovulation induction, oocyte retrieval was performed. Following this procedure, a capsule containing 200 mg of natural progesterone (Progestan, Kocak Farma, Istanbul) was applied vaginally three times per day to support the luteal phase.

The number of retrieved oocytes, the number of meiosis II (MII) oocytes, the number of embryos formed, and the clinical pregnancy rates were documented. The presence of pregnancy was determined by measuring the level of hCG in the serum 12 to 14 days after oocyte retrieval. The presence of an intrauterine gestational sac and the detection of a fetal heartbeat by ultrasonography were used to define clinical pregnancy.

Statistical Analysis

The statistical analyses were performed using *Statistical Package for the Social Sciences version 15.0* (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to determine the distribution of the data. One-way ANOVA analysis of continuous and normally distributed variables was preferred and expressed as mean ± standard deviation (SD). The Kruskal Wallis test was used for the analysis of continuous variables that did not show normal distribution and was shown as the median (minimum-maximum). Categorical variables are represented as percentages (numbers). Using Chi-square or Fischer-Exact tests, the differences between categorical data were evaluated. In this analysis of correlations between measurements, Pearson or Spearman correlation analyses were utilized as appropriate. P values below 0.05 were regarded as statistically significant.

Results

This study was accomplished with the participation of 88 infertile women who conformed to the inclusion criteria and received IVF treatment. Table I compares the demographic and clinical characteristics of the population subject to study. The comparison of the mean ages of the different study groups found statistically significant differences between the NOR

Table I. Comparison of demographic and clinical characteristics of study groups

	NOR Grubu (Grup 1) (n=42)	DOR Grubu (Grup 2) (n=22)	PKOS Grubu (Grup 3) (n=24)	*p*		
				1 vs 2	1 vs 3	2 vs 3
Age (years)	29.8±5.2	34.6±5.2	29.6±4.4	*0.001**	*0.984*	*0.002**
VKİ (kg/m²)	24.7 (23.1-28.4)	24.9 (21.9-28.2)	23.6 (21.9-27.1)	*0.427*		
BAsal E2 (pg/mL)	42.1 (34.7-55.1)	47.7 (33.1-63.4)	49.2 (32.7-57.8)	*0.620*		
Basal FSH (IU/L)	7.2±1.3	9.4±1.4	5.4±1.2	*0.121*	*0.249*	*0.006**
Basal LH (IU/L)	5.7 (4.3-7.3)	6.3 (3.7-10.5)	7.8 (4.7-10.9)	*0.150*		
AMH (ng/ml)	2.8±1.4	0.6±0.2	7.3±2.1	*<0.001**	*<0.001**	*<0.001**
GDF-15	390.0±125.6	268.4±120.3	331.5±110.0	*0.696*		
Number of oocytes retrieved (n)	9.6±2.6	4.8±1.3	12.0±4.4	*<0.001**	*0.140*	*<0.001**
MII oocyte number (n)	7.1±1.7	3.5±1.9	8.7±2.7	*0.011**	*0.365*	*<0.001**
Number of embryos (n)	4.29±1.4	1.68±0.4	5.88±1.8	*0.016**	*0.183*	*<0.001**
Clinical pregnancy (n,%)	14 (33.3%)	3 (13.6%)	11 (45.8%)	*0.078*	*0.314*	*0.026**

ABBREVIATIONS: NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndrome, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, AMH: anti-Mullerian hormone, GDF: Growth diffentiation factor, MII: Meiosis II. *$p<0.05$ value was accepted as statistical significance

and DOR groups, as well as the NOR and PCOS groups ($p=0.001$ and $p=0.002$, respectively).

The mean age of the DOR group was higher than that of the NOR and PCOS groups, as predicted. There was no statistically significant difference ($p>0.05$) between the medians of BMI, basal E2, and basal LH levels between the three study groups. Nevertheless, the mean FSH at baseline was considerably higher in the DOR group compared to the PCOS group ($p=0.006$). Consistent with previous findings, the median serum AMH levels in all three groups exhibited statistically significant differences ($p<0.001$, $p<0.001$, $p<0.001$). The PCOS group has the greatest AMH levels, whereas the DOR group has the lowest AMH levels. Regarding serum GDF-15 concentrations, none of the three study groups exhibited statistically significant mean values ($p>0.05$). The NOR group had higher values for the mean total number of oocytes, MII numbers, and embryos obtained after the *Oocyte pick-up* procedure than the DOR group ($p0.001$, $p=0.011$, and $p=0.016$, respectively). Once more, it has been shown that the PCOS group exhibits significantly higher values compared to the DOR group for the given parameters ($p<0.001$, $p<0.001$, and $p<0.001$). Statistically, only participants in the PCOS group had a significantly higher clinical pregnancy rate than those in the DOR group ($p=0.026$).

The analysis of the connection between serum GDF-15 level and other research parameters is displayed in Table II. Serum GDF-15 levels were not correlated with age, BMI, serum E2, FSH, or AMH levels. It was determined that study parameters such as the number of oocytes retrieved, the number of MII oocytes, and the clinical pregnancy rate were not statistically significantly correlated with serum GDF-15 levels.

However, only in the DOR group were GDF-15 levels significantly and moderately correlated ($r=0.430$, $p=0.046$) with serum LH level and significantly and highly correlated ($r=0.633$, $p=0.001$) with the number of embryos.

Discussion

The objective of this study was to examine the correlation between serum GDF-15 levels and clinical outcomes among women undergoing IVF therapy, categorized by their ovarian reserve types. In terms of serum GDF-15 levels, there was no significant difference between the three ovarian reserve groups. However, statistically significant, and positive correlations were found with serum GDF-15 concentration, serum LH level, and embryo number only in women in the DOR group. Based on our analysis, no other study with regard to this subject matter has been identified in the existing literature.

In some animal studies, an increase in plasma GDF-15 levels has been linked to mitochondrial dysfunction and excessive oxidative activity (15,16). An increase in GDF-15 expression is observed as a result of the increase in reactive oxygen species caused by ageing (17). Therefore, it has been suggested that GDF-15 may serve as a biomarker for biological ageing and mitochondrial dysfunction in healthy

humans (2,17,18). GDF-15 is thought to function as a protective mechanism against tissue damage (19). Multiple research studies have linked ageing to chronic low-grade inflammation (20). Unfortunately, the results of our investigation did not reveal a statistically significant association between blood GDF-15 levels and the study groups.

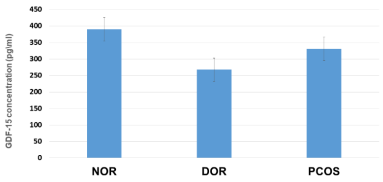
Table II. Correlation analysis of serum GDF-15 level with other study parameteopurs

	NOR Grubu (n=42)		DOR Grubu (n=22)		PKOS Grubu (n=24)	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	-0.238	*0.129*	-0.035	*0.878*	-0.393	*0.057*
VKİ (kg/m²)	0.150	*0.343*	-0.308	*0.163*	0.113	*0.600*
Basal E2 (pg/mL)	0.037	*0.817*	0.287	*0.195*	0.025	*0.908*
Basal FSH (IU/L)	-0.081	*0.410*	0.183	*0.415*	0.153	*0.477*
Basal LH (IU/L)	-0.024	*0.879*	0.430	*0.046**	0.006	*0.979*
AMH (ng/ml)	0.086	*0.589*	0.415	*0.055*	0.025	*0.908*
Number of oocytes retrieved (n)	0.097	*0.543*	-0.090	*0.691*	-0.032	*0.883*
MII oocyte number (n)	0.038	*0.812*	0.200	*0.373*	0.027	*0.900*
Number of embryos (n)	0.128	*0.420*	0.633	*0.002**	0.124	*0.565*
Clinical pregnancy	-0.216	*0.169*	0.093	*0.680*	0.228	*0.284*

NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndrome, BMI: Body mass index, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, AMH: anti-Mullerian hormone, GDF: Growth diffentiation factor, MII: Meiosis II. *p<0.05 value was accepted as statistical significance.

It is known that there is an increase in GDF-15 expression in response to different stimuli such as oxygen deprivation (such as oxidative stress, hypoxia, and anoxia) and acute tissue damage (21,22)GDF-15 functions as an autocrine anti-inflammatory and tissue repair factor that is released in proportion to acute and chronic tissue injury, although the exact mechanism is unknown (21–23). In this context, the hypothesis that the DOR status of infertile women and the perception of tissue damage by their bodies may exist. Thus, as a result of this perception, a compensatory mechanism may have been found to correlate with the increase in GDF-15 level and the number of embryos in women with DOR, as in our study.

Figure 1. GDF-15 levels of the groups



NOR: Normal ovarian reserve, DOR: Diminished ovarian reserve, PCOS: Polycystic ovary syndr

Under physiological conditions, the only tissue with a high GDF-15 concentration is the placenta. Both the placenta and fetal membranes contain GDF-15. This indicates that GDF-15 has a role at the maternal-fetal interface (24). In addition, the hypothesis that GDF-15 is effective in the feto-maternal immunotolerance process is accepted (25). Plasma concentrations of GDF-15 reach high levels during pregnancy and are believed to play a crucial role in maintaining pregnancy (26). According to numerous studies, reduced GDF-15 levels in early pregnancy can predict an abortion (27,28)noted to have a confirmed viable fetus, but subsequently miscarry. METHODS We performed a prospective cohort study, recruiting 462 women in the first trimester presenting to EPAU and had fetal viability confirmed by ultrasound. We obtained plasma samples on the same day and measured MIC-1, PAPP-A and human chorionic gonadotrophin (hCG. In this study, we found a significant and strong correlation between serum GDF-15 levels and the number of embryos formed in women in the DOR group.

One notable disadvantage of this study is the only assessment of GDF-15 in the serum of participants, which was mostly due to financial limitations. Ideally, serum and follicular fluid samples should be used to test GDF-15 together. Thus, correlations between serum and follicular fluid levels of GDF-15 will also be observed. One further limitation of this research is the comparatively limited sample size of participants. Nonetheless, this is the first known study to investigate the correlation between serum GDF-15 levels and the clinical outcomes of IVF treatments. This aspect of our investigation makes it significant.

According to the study's findings, there is a significant and strong correlation between serum GDF-15 concentration and the number of embryos formed as a consequence of IVF treatment. The serum GDF-15 level can therefore be considered a biomarker for predicting the clinical outcomes of IVF treatments. It is evident that conducting prospective research with a substantial number of participants is

necessary in order to establish significant associations with clinical pregnancy outcomes.

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References

1. Good C, Tulchinsky M, Mauger D, Demers LM, Legro RS. Bone mineral density and body composition in lean women with polycystic ovary syndrome. Fertil Steril 1999;72:21–25.
2. Berberoglu Z, Aktas A, Fidan Y, Yazici AC, Aral Y. Association of plasma GDF-9 or GDF-15 levels with bone parameters in polycystic ovary syndrome. J Bone Miner Metab 2015;33:101–108.
3. O'Brien Y, Kelleher C, Wingfield M. "So what happens next?" exploring the psychological and emotional impact of anti-Mullerian hormone testing. J Psychosom Obstet Gynaecol 2020;41:30–37.
4. Ulrich ND, Marsh EE. Ovarian Reserve Testing: A Review of the Options, Their Applications, and Their Limitations. Clin Obstet Gynecol 2019;62:228–237.
5. Bootcov MR, Bauskin AR, Valenzuela SM, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A 1997;94:11514–11519.
6. Mimeault M, Batra SK. Divergent molecular mechanisms underlying the pleiotropic functions of macrophage inhibitory cytokine-1 in cancer. J Cell Physiol 2010;224:626–635.
7. Kempf T, Eden M, Strelau J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res 2006;98:351–360.
8. Kleinert M, Clemmensen C, Sjøberg KA, et al. Exercise increases circulating GDF15 in humans. Mol Metab 2018;9:187–191.
9. Nazarova NI, Chikhirzhina GI, Tuohimaaa P. Transcriptional regulation of placental transforming growth factor-beta by calcitriol in prostate cancer cells is androgen-independent. Mol Biol 2006;40:84–89.
10. Bauskin AR, Jiang L, Luo XW, Wu L, Brown DA, Breit SN. The TGF-beta superfamily cytokine MIC-1/GDF15: secretory mechanisms facilitate creation of latent stromal stores. J Interferon Cytokine Res 2010;30:389–397.
11. Serdyńska-Szuster M, Jędrzejczak P, Ożegowska KE, Hołysz H, Pawelczyk L, Jagodziński PP. Effect of growth differentiation factor-9 C447T and G546A polymorphisms on the outcomes of in vitro fertilization. Mol Med Rep 2016;13:4437–4442.
12. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril 2015;103:e9–e17.
13. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–47.
14. Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L, ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011;26:1616–1624.
15. Davis RL, Liang C, Sue CM. A comparison of current serum biomarkers as diagnostic indicators of mitochondrial diseases. Neurology 2016;86:2010–2015.
16. Fujita Y, Taniguchi Y, Shinkai S, Tanaka M, Ito M. Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders. Geriatr Gerontol Int 2016;16 Suppl 1:17–29.
17. Conte M, Ostan R, Fabbri C, et al. Human Aging and Longevity Are Characterized by High Levels of Mitokines. J Gerontol A Biol Sci Med Sci 2019;74:600–607.
18. Tanaka T, Biancotto A, Moaddel R, et al. Plasma proteomic signature of age in healthy humans. Aging Cell 2018;17:e12799.
19. Assadi A, Zahabi A, Hart RA. GDF15, an update of the physiological and pathological roles it plays: a review. Pflugers Arch 2020;472:1535–1546.
20. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 2014;69 Suppl 1:S4-9.
21. Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting.. Hum. Reprod 2011.
22. Aljanabi S. Universal and rapid salt-extraction of high quality genomic DNA for PCR- based techniques. Nucleic Acids Res 1997;25:4692–4693.
23. Farquhar C, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. Cochrane database Syst Rev 2018;8:CD010537.
24. Hromas R, Hufford M, Sutton J, Xu D, Li Y, Lu L. PLAB, a novel placental bone morphogenetic protein.

Biochim Biophys Acta 1997;1354:40–44.
25. Xiong Y, Walker K, Min X, et al. Long-acting MIC-1/GDF15 molecules to treat obesity: Evidence from mice to monkeys. Sci Transl Med 2017;9.
26. Moore AG, Brown DA, Fairlie WD, et al. The transforming growth factor-ss superfamily cytokine macrophage inhibitory cytokine-1 is present in high concentrations in the serum of pregnant women. J Clin Endocrinol Metab 2000;85:4781–4788.
27. Kaitu'u-Lino TJ, Bambang K, Onwude J, Hiscock R, Konje J, Tong S. Plasma MIC-1 and PAPP-a levels are decreased among women presenting to an early pregnancy assessment unit, have fetal viability confirmed but later miscarry. PLoS One 2013;8:e72437.
28. Lyu C, Ni T, Guo Y, et al. Insufficient GDF15 expression predisposes women to unexplained recurrent pregnancy loss by impairing extravillous trophoblast invasion. Cell Prolif 2023;e13514.

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The Effect of Shoulder Pain on Sleep Quality

Omuz Ağrısının Uyku Kalitesine Etkisi

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The Effect of Shoulder Pain on Sleep Quality

Abstract

Objective: Shoulder pain, a musculoskeletal issue, is most prevalent in patients aged 50-59. It can cause sleep problems and reduce sleep quality. We aimed to explore the relationship between sleep quality, pain, and disability in patients with shoulder pain, despite limited literature on this issue.

Material and Method: Study involved ninety-one patients aged 18-80 with persistent shoulder pain sought out at a physical medicine and rehabilitation outpatient clinic. Factors such as age, gender, education level, symptom duration, body mass index (BMI), occupation, and pain severity were recorded. Severity of pain was assessed using the visual analogue scale (VAS), pain and disability using the Shoulder Pain and Disability Index (SPADI), and sleep quality using the Pittsburgh Sleep Quality Index (PSQI).

Results: The mean age was 54.9 (±10.5). There were 28% men and 63% women among the patients. Fourteen percent of the patients had heavy work above shoulder level. A positive correlation was detected between PSQI and VAS and SPADI (*p value 0.004* and *0.003, respectively*) (correlation coefficient 0.304 and 0.305, respectively). No significant relationship was found between PSQI and BMI and symptom duration (*p value 0.464 and 0.718, respectively*) (*correlation coefficient 0.08 and 0.039, respectively*). While there was a significant difference in SPADI values between two groups with and without heavy work above the shoulder level, no significant difference was detected in PSQI values (*p value 0.021 and 0.36, respectively*).

Conclusion: We found that the patient's VAS and SPADI values and sleep quality were negatively related to shoulder pain. Sleep disturbance due to pain at night can also affect daytime disability. Pain and sleep quality disorders can enter a vicious circle.

Keywords: Musculoskeletal system, shoulder pain, sleep quality.

Özet

Amaç: Bir kas-iskelet sistemi sorunu olan omuz ağrısı, en çok 50-59 yaş aralığında görülür. Omuz ağrısı, uyku sorunlarına yol açarak uyku kalitesini düşürebilir. Literatürde omuz ağrısı ve uyku kalitesi ile ilgili yeterli çalışmaya rastlanmadığından omuz ağrılı hastalarda uyku kalitesi ve uykunun ağrı ve dizabilite ile ilişkisini incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya omuz ağrısı şikayetiyle fizik tedavi ve rehabilitasyon polikliniğine başvuran 18-80 yaş arası 91 hasta dahil edildi. Yaş, cinsiyet, eğitim düzeyi, semptom süresi, vücut kitle indeksi (VKİ), meslek, ağrı şiddeti kaydedildi. Ağrının şiddeti vizüel analog skala (VAS), ağrı-disabilite Omuz Ağrısı ve Disabilite İndeksi (SPADI) ve uyku kalitesi Pittsburgh Uyku Kalite İndeksi (PUKİ) kullanılarak değerlendirildi.

Bulgular: Ortalama yaş 54,9 (±10,5) idi. Hastaların %63'ü kadın, %28'i erkekti. Bunların %14'ü omuz hizasının üzerinde ağır işlerde çalışıyordu. PUKİ ile VAS ve SPADI arasında pozitif bir korelasyon tespit edildi (sırasıyla *p değeri 0,004 ve 0,003*) (*korelasyon katsayısı 0.304 ve 0.305*, sırasıyla) . PUKİ ile VKİ ve semptom süresi arasında anlamlı bir ilişki bulunamadı *(sırasıyla p değeri 0,464 ve 0,718*) (*korelasyon katsayısı 0.08 ve 0.039*, sırasıyla). Omuz seviyesi üzeri ağır iş yapan ve yapmayan iki grup arasında SPADI değerlerinde anlamlı fark bulunurken, PUKİ değerlerinde anlamlı fark saptanmadı (sırasıyla *p değeri 0,021 ve 0,36*).

Sonuç: Hastanın VAS ve SPADI değerleri ile uyku kalitesinin omuz ağrısı ile negatif ilişkili olduğunu bulduk. Gece ağrıya bağlı uyku bozukluğu gündüz disabiliteyi de etkileyebilir. Ağrı ve uyku kalitesi bozuklukları bir kısır döngüye girebilmektedir.

Anahtar Sözcükler: Kas-iskelet sistemi, omuz ağrısı, uyku kalitesi.

Introduction

One of the most prevalent musculoskeletal system concerns is shoulder pain (1). The joint and the soft tissues around are the source of pain (2). The underlying causes of this common symptom of Physical Medicine and Rehabilitation practice include rotator cuff problems, adhesive capsulitis, calcific tendinitis, acromioclavicular joint degenerations, glenohumeral joint osteoarthritis, and glenohumeral instability (3). In the general population, shoulder pain that causes limitation is prevalent at a rate of 20% (4). It is known that shoulder pain is most common between the ages of 50-59, however, due to a reduction in physical activity, a lack of exercise, increased computer usage, and increased smartphone use, shoulder pain in young people is progressively escalating (5,6).

The future prospects for shoulder pain varies; 40–50% of patients report continuing discomfort 6–12 months after initial symptoms come up (7). The biological processes, physiological recuperation, learning, memory, cognitive activities, and emotional well-being are all significantly impacted by sleep (8). The incidence of sleep problems in the general adult population ranges from 15% to 20%, making it one of the most prevalent health conditions (9).

Inability to fall asleep or stay asleep due to shoulder pain might result in sleep issues. It can reduce sleep quality, and shifting positions while sleeping can also worsen shoulder pain (10). Shoulder pain may cause awakening from sleep (11). Reduced sleep duration and quality might have an impact on the shoulder muscle's ability to relax and repair (12).

Most of the time, sleep disorder is one of the main reasons that direct the patient to shoulder surgery. Generally, in contrast to loss of shoulder function, patients' complaints are nighttime soreness that, in the near term, disrupts sleep. Shoulder pain and persistent problematic posture during the night have a particular negative impact on sleep quality (13). Important complaints that have an intricate relationship with one another and impact the person's bodily and behavioral health are pain and sleep disruption. Chronic pain frequently interferes with sleep and might make it difficult to function during the day. Proper identification and treatment of sleep issues can help break this vicious cycle by relieving pain symptoms (14).

There is very little information about this problem in the literature. We aimed to examine sleep quality, and the relationship between sleep, and pain and disability in patients with shoulder pain.

Material and Method

Ethics committee approval of the local institute was received for the study (date: 16.05.23 Decision no: 05) and it was conducted in accordance with the principles of the Declaration of Helsinki. The study procedure was explained to the participants and consent was obtained. Ninety-one patients between the ages of 18 and 80, who consecutively applied to the physical medicine and rehabilitation (PMR) outpatient clinic with complaints of shoulder pain that had persisted for at least 3 months, were included. Exclusion criteria are: 1-) history of surgery or infection on the affected shoulder, 2-) pregnancy, 3-) history of neurological or rheumatic disease (such as rheumatoid arthritis) or malignancy, 4-) uncontrolled diabetes mellitus (DM), hypertension (HT) or patients with heart/lung disease, 5-) cervical radicular pain, 6-) morbid obesity and sleep apnea, and 7) psychiatric disease.

The patients' age, gender, education level, symptom duration (3-6 months, 6-12 months and longer than 12 months), body mass index (BMI), occupation (those with or without a profession above shoulder level) information were recorded. Plasterers, assembly line workers, and construction workers who performed heavy lifting at shoulder level were among the professional groups that were included.

The severity of shoulder pain was evaluated with the visual analogue scale (VAS). Pain and disability were evaluated with Shoulder Pain and Disability Index (SPADI). Sleep quality was evaluated with Pittsburgh Sleep Quality Index (PSQI). Pain intensity was assessed using a standard 10-cm VAS; at one end, 0 meant "no pain," and at the other end, 10 meant "unbearable pain" (15). Shoulder functional status was assessed using SPADI, which consists of 5 items assessing pain and 8 items assessing disability. The score ranges from 0% to 100%; A higher score indicates more pain and disability (16). SPADI has pain and activity limitation subparameters and a total score. The pain subparameter consists of 5 questions about shoulder pain during daily living activities, and the activity limitation consists of 8 questions about difficulty in performing daily living activities. Responses are marked numerically by patients between 0 and 10, and the scores of all responses are summed and divided by the number of questions in that subparameter to determine the value of each subparameter. The total SPADI score is determined by averaging the 2 subparameter scores. A high score indicates increased pain and impaired shoulder functions (17,18).

PSQI allows evaluating sleep quality, amount of sleep, and the presence and severity of sleep

disorders in the last 1 month. This scale consists of 7 subcomponents; subjective sleep quality, time to fall asleep, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping pills, and daytime dysfunction. The total PSQI score is obtained by summing the 7 subscores and ranges from 0 to 21 points. PSQI total score indicates good sleep quality (≤5) and poor sleep quality (>5) (19,20).

Statistical Analysis

Data analysis was done with the SPSS for Windows 22.0 package program. Whether continuous variables showed a normal distribution was examined with the Shapiro Wilks test. Descriptive statistics were shown as mean ± standard deviation or median (minimum-maximum) for continuous variables, and as number of observations and (%) for nominal variables. The significance of the difference between the paired groups in terms of all parameters and continuous variables was investigated with the Student's t-test. The correlations were evaluated with Pearson correlation tests. Results were considered significant for $p<0.05$.

Results

The mean age was 54.9 (±10.5). There were 28% men and 63% women among the patients. Fourteen percent of the patients had heavy work above shoulder level (Table I). A positive correlation was detected between PSQI and VAS and SPADI (Table II). No significant relationship was found between PSQI and BMI and symptom duration (Table II). While there was a significant difference in terms of SPADI values between the group with heavy work above the shoulder level and the group without, there was no significant difference in terms of PSQI values (Table III).

Discussion

In our study where we aimed to examine sleep quality, and its relationship with pain and disability in patients with shoulder pain, we found that pain and disability increase when sleep quality is poor. In general, the incidence of shoulder pain in women is higher than in men, and the psychological stress in particular is directly linked to shoulder pain in women. (21).

In the study of Akalin et al. (3), it was reported that 68% of the patients were female and 32% were male. It was similar for us too. The mean age was found to be 55.16 in this study, and the mean age of our patients was found to be 54.9, which was similar to this study. There were 28% men and 63% women among the patients. Fourteen percent of the patients had heavy work above shoulder level. The mean age and female gender predominance were found to be consistent with the literature.

Table I. Demographic data and VAS, SPADI, PSQI

	N=91
Age mean (SD)	54.89(10.5)
Gender n (%)	
Female	63(69.2)
Male	28 (30.8)
Symptom duration n (%)	
3-6 months	34(37.4)
6-12 months	17(18.7)
>12 months	40(44)
BMI	30.0 (6.8)
Education (%)	
Illiterate	14(15.4)
Primary school	42(46.2)
Middle school	5(5.5)
High school	16(17.6)
College	2(2.2)
University	12(13.2)
Occupation	
Severe heat above shoulder level	14 (15.4)
No heavy heat above shoulder level	77 (84.6)
VAS mean (SD)	6.69(1.74)
SPADI mean (SD)	66.2(17.4)
PSQI mean (SD)	8.3(4.4)

BMI: Body mass index; VAS: Visual analog scale; SPADI: Shoulder pain and disability index; PSQI: Pittsburgh sleep quality index

It is known that more than 40% of patients state that their pain has been present for more than 12 months when they consult a physician (22). In 44% of our patients, the pain complaint continued for more than 12 months. The severity of a woman's shoulder limitations increases with the severity of her shoulder pain (23). Sleep may be a period when shoulder muscles relax and recover. However, if sleep is of low quality, shoulder muscles cannot unwind and recuperate, which may cause shoulder problems during the day (11,12). Therefore, it is possible to expect that shoulder issues will be decreased if a technique is used to enhance sleep quality in addition to shoulder pain reduction measures (23).

While the mean PSQI of the patients in the study of Tekeoğlu et al. (11) was 11.6, the mean PSQI of the patients in the study of Edward P. et al. (24) was 8.59. We found the mean PSQI to be 8.3. In a cross-

sectional investigation of the associations between middle-aged women's sleep quality, neck discomfort, shoulder pain and disability, physical activity, and health perception, the total PSQI mean score was found to be 8.88 (25). While there was a significant difference in terms of SPADI values between the group with heavy work above the shoulder level and the group without, there was no significant difference in terms of PSQI values.

Table II. Correlations

	VAS	SPADI	BMI	Symptom duration
	r/p	*r/p*	*r/p*	*r/p*
PSQI*	*0.304/0.004*	*0.305/0.003*	*0.08/0.464*	*0.039/0.718*

r: correlation coefficient; VAS: Visual analog scale; SPADI: Shoulder pain and disability index; PSQI: Pittsburgh sleep quality index
*: Pearson corelation test

The levels of cytokines and inflammatory mediators are elevated by insufficient sleep (26,27). Inflammation may mediate the relationship between poor sleep quality and quantity, other psychological risk factors, and neck, shoulder, and low back disorders, according to research (28) showing that chronic stress, obesity, and smoking also increase the concentration of inflammatory factors. It is known that obesity is a factor that negatively affects sleep quality (29,30). We did not detect a significant relationship between PSQI and BMI. A study showed that obesity may negatively affect sleep quality and daily living activity scores in patients with neck pain due to myofascial pain syndrome (31). Khazzam et al. (8) in their study evaluating the sleep quality of their patients with rotator cuff lesions, they reported that they could not find a correlation between poor sleep quality and the lesion, and that poor sleep quality was associated with depression. We found a positive correlation between sleep quality and VAS and SPADI. However, we did not detect a significant relationship between symptom duration and sleep quality. Austin stated that poor sleep quality may be related to pain levels in patients with rotator cuff lesions (32). Khazzam et al. (8) pinpointed specific characteristics such female gender, depression, the prevalence of low back pain, diabetes, cervical involvement, and high body mass index as being connected to poor sleep quality.

Holdaway et al. discovered that high-risk sleeping postures (free fall and starfish) were protective in their cross-sectional investigation comparing sleeping positions with shoulder discomfort (33). We did not question sleep position in our study. Longo et al. (34) showed that after rotator cuff repair, sleep disorders improved three to six months after surgery and quality of life increased.

Ansok et al. (35), in their study on objective sleep measurements, showed that sleep quality was poor, sleep duration was short, they woke up frequently, and productivity decreased in patients with rotator cuff tear. A recent study by Ha et al. (36) suggested that melatonin levels, which peak at night and in the early morning hours, may activate the inflammatory response and serve as a mediator that exacerbates pain complaints.

Table 3. Groups with and without heavy work above shoulder level
Comparison with SPADI and PSQI

Variable	Heavy work above shoulder level(n=14)	No heavy work above shoulder level (n=77)	*p**
SPADI mean(±SD)	56.4(±18.8)	68.01(±16.6)	*0.021*
PSQI mean(±SD)	6(±4.9)	8.7(±4.2)	*0.36*

SPADI: Shoulder pain and disability index; PSQI: Pittsburgh sleep quality index
*:Student t test

Recent studies have investigated the impact of mood and emotional experiences on sleep and pain-related behavioral symptoms (37,38). We did not include those with a history of psychiatric illness in our study. Sleep quality has been demonstrated to have a negative link with health perception and a favorable association with neck, shoulder, and disability pain (25). Similarly, we found a positive correlation between PSQI and VAS and SPADI.
Recent studies have demonstrated that rotator cuff repair patients who have surgery experience less insomnia and higher levels of sleep quality than the general population (32,39). Poor sleep quality is an important problem not only in shoulder pain but also in other musculoskeletal problems such as low back and neck.

Karatas et al. (40) observed that sleep quality was significantly impaired in patients with carpal tunnel syndrome (CTS) compared to healthy controls. Poor sleep quality was also discovered in those with mechanical neck pain (PSQI>8) (41). According to studies, those with persistent low back pain who have poor sleep have more intense pain (42,43). Intuitively, it seems sense that a poor night's sleep

would affect a person's regular circadian cycle. Sleep is a natural aspect of life for everyone. A restful night's sleep helps the body to regenerate and recover while keeping the mind's attitude and perspective in the right place. There are suggestions that identifying people with problematic shoulders who complain about their ability to sleep well would be a crucial initial step in developing a treatment strategy for this impairment (24).

The limitations of our study are the lack of a control group and our cross-sectional evaluation, as well as the insufficient number of patients. However, we think that it is important to draw attention to the fact that sleep quality is also a part of the evaluation in the evaluation of patients with shoulder pain.

Conclusion

We found that the patient's VAS and SPADI values and sleep quality were negatively related to shoulder pain. Sleep disturbance due to pain at night can also affect daytime disability. Pain and sleep quality disorders can enter a vicious circle.

References

1. Djade CD, Porgo TV, Zomahoun HTV, Perrault-Sullivan G, Dionne CE. Incidence of shoulder pain in 40 years old and over and associated factors: A systematic review. Eur J Pain. 2020; 24:39-50.
2. Murphy RJ, Carr AJ. Shoulder pain. BMJ Clin Evid. 2010; 07:1107.
3. Akalın E, El Ö, Bircan Ç, et al. Omuz Problemi Olan Hastaların Genel Özellikleri. Dokuz Eylül Üniversitesi Tıp Fakültesi Dergisi. 2006; 20:75-78.
4. Meislin RJ, Sperling JW, Stitik TP. Persistent shoulder pain: epidemiology, pathophysiology, and diagnosis. Am J Orthop. 2005; 34: 5-9.
5. Hee-hyeon K, Dong-ho L. Comparative analysis of pain disorder factors and subjective pain reduction effect after functional adjustment procedure therapy for shoulder pain patients. J Korean Soc Phys Med. 2020; 15:87–99.
6. Health Insurance Review & Assessment Service. Three major diseases that cause shoulder pain. 2020. [cited January 1, 2022]. Available at: https://www.korea.kr/news/healthView.do?newsId=148873773 [access date October 5, 2022].
7. Laslett M, Steele M, Hing W, McNair P, Cadogan A. Shoulder pain patients in primary care–part 1: Clinical outcomes over 12 months following standardized diagnostic workup, corticosteroid injections, and community-based care. J Rehabil Med. 2014; 46:898-907.
8. Khazzam MS, Mulligan EP, Brunette-Christiansen M, Shirley Z. Sleep Quality in Patients with Rotator Cuff Disease. J. Am Acad Orthop Surg. 2018; 26:215–222.
9. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. Sleep Med. Rev. 2016; 25:52–73.
10. Park SY, Choi TS, Kim DH, Ryu BH, Lee SB. Correlation between neck and shoulder pain, neck and shoulder disability, headache and smartphone addiction in adults with sleep disorders. J Korean Soc Phys Med. 2020; 15:43–50.
11. Tekeoglu I, Ediz L, Hiz O, Toprak M, Yazmalar L, Karaaslan G. The relationship between shoulder impingement syndrome and sleep quality. Eur Rev Med Pharmacol Sci. 2013; 17:370-374.
12. Canivet C, Ostergren PO, Choi B, et al. Sleeping problems as a risk factor for subsequent musculoskeletal pain and the role of job strain: results from a one-year follow-up of the Malmö Shoulder Neck Study Cohort. Int J Behav Med. 2008; 15:254-62.
13. Longo UG, Facchinetti G, Marchetti A, et al. Sleep Disturbance and Rotator Cuff Tears: A Systematic Review. Medicina (Kaunas) 2019; 55:453.
14. Benca RM, Ancoli-Israel S, Moldofsky H. Special considerations in insomnia diagnosis and management: depressed, elderly, and chronic pain populations. J Clin Psychiatry. 2004; 65:26-35.
15. Boonstra AM, Schiphorst Preuper HR, Balk GA, Stewart RE. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. Pain. 2014; 155:2545–2550.
16. Paul A, Lewis M, Shadforth MF, Croft PR, Van Der Windt DA, Hay EM. A comparison of four shoulder-specific questionnaires in primary care. Ann Rheum Dis. 2004; 63:1293–1299.
17. Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. Arthritis Care Res. 1991; 4:143-9.
18. Bicer A, Ankaralı H. Shoulder pain and disability index: a validation study in Turkish woman. Singapore Mefd J. 2010; 51:865-870.
19. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric prac- tice and research. Psychiatry Res. 1989; 28:193-213.
20. Agarguun MY, Kara H, Anlar OO. The validity and reliability of the Pittsburgh sleep quality index. Turk Psikiyatri Dergisi. 1996; 7:107- 115.
21. van Doorn PF, de Schepper EIT, Rozendaal RM, et al. The incidence and management of shoulder complaints in general practice: a retrospective cohort study. Fam Pract. 2021; 38:582-588.

22. van der Heijden G. Shoulder disorders: a state-of-the-art review. Bailliere's Clin Rheum. 1999; 13:287-309.
23. Hwang Y, Oh J. The relationship between shoulder pain and shoulder disability in women: The mediating role of sleep quality and psychological disorders. Medicine (Baltimore). 2022; 101: e31118.
24. Mulligan EP, Brunette M, Shirley Z, Khazzam M. Sleep quality and nocturnal pain in patients with shoulder disorders. Journal of shoulder and elbow surgery, 2015; 24:1452–1457.
25. Lee MK, Oh J. The relationship between sleep quality, neck pain, shoulder pain and disability, physical activity, and health perception among middle-aged women: a cross-sectional study. BMC Womens Health. 2022; 22:186.
26. Irwin M. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav Immun. 2002; 16:503–512.
27. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004; 43:678–683.
28. Ranjit N, Diez-Roux AV, Shea S, Cushman M, Seeman T, Jackson SA, Ni H. Psychosocial factors and inflammation in the multi-ethnic study of atherosclerosis. Arch Intern Med. 2007; 167:174–181.
29. Ferranti R, Marventano S, Castellano S, et al. Sleep quality and duration is related with diet and obesity in young adolescent living in Sicily, Southern Italy. Sleep Sci. 2016; 9:117- 122.
30. Fatima Y, Doi SA, Mamun AA. Sleep quality and obesity in young subjects: a meta-analysis. Obes Rev. 2016; 17:1154-1166.
31. Ural FG. Miyofasiyal ağrı sendromu olan hastalarda obezitenin uyku kalitesi ve günlük yaşam aktiviteleri üzerine etkisi. Cukurova Medical Journal. 2018; 43:600-604.
32. Austin L, Pepe M, Tucker B, et al. Sleep disturbance associated with rotator cuff tear: correction with arthroscopic rotator cuff repair. The American journal of sports medicine 2015; 43: 1455-1459.
33. Holdaway LA, Hegmann KT, Thiese MS, Kapellusch J. Is sleep position associated with glenohumeral shoulder pain and rotator cuff tendinopathy: A cross-sectional study. BMC Musculoskelet. Disord. 2018; 19:408.
34. Longo UG, Candela V, De Salvatore S, et al. Arthroscopic Rotator Cuff Repair Improves Sleep Disturbance and Quality of Life: A Prospective Study. Int J Environ Res Public Health. 2021; 18:3797.
35. Ansok CB, Khalil LS, Muh S. Objective assessment of sleep quality in patients with rotator cuff tears. Orthopaedics & traumatology, surgery & research: OTSR. 2020; 106:61–66.
36. Ha E, Lho YM, Seo HJ, Cho CH. Melatonin plays a role as a mediator of nocturnal pain in patients with shoulder disorders. J Bone Joint Surg Am. 2014; 96:e108-131.
37. Hamilton NA, Affleck G, Tennen H, et al. Fibromyalgia: the role of sleep in affect and in negative event reactivity and recovery. Health Psychol 2008; 27: 490-497.
38. Belt NK, Kronholm E, Kauppi MJ. Sleep problems in fibromyalgia and rheumatoid arthritis compared with the general population. Clin Exp Rheumatol. 2009; 27: 35-41.
39. Cho C, Song K, Hwang, et al. Does Rotator Cuff Repair Improve Psychologic Status and Quality of Life in Patients With Rotator Cuff Tear? Clin Orthop Relat Res. 2015; 473:3494-3500.
40. Karatas G , Kutluk O, Akyuz M, Karaahmet OZ, Yalcin E. The effects of carpal tunnel syndrome on sleep quality. Ann Med Res 2020;27(1):381-7
41. Muñoz-Muñoz S, Muñoz-García MT, Alburquerque-Sendín F, Arroyo-Morales M, Fernández-de-las-Peñas C. Myofascial trigger points, pain, disability, and sleep quality in individuals with mechanical neck pain. J Manipulative Physiol Ther. 2012; 35:608-613.
42. Ruiz-Sáez M, Fernández-de-las-Peñas C, Blanco CR, Martí- nez-Segura R, García-León R. Changes in pressure pain sensitivity in latent myofascial trigger points in the upper trapezius muscle after a cervical spine manipulation in pain- free subjects. J Manipulative Physiol Ther. 2007; 30:578-583.
43. Marin R, Cyhan T, Miklos W. Sleep disturbance in patients with chronic low back pain. Am J Phys Med Rehabil. 2006; 85:430-435.

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Küçük Hücre Dışı Akciğer Kanserli Hastalarda FDG PET/BT Parametrelerinin Evre ve Patolojik Veriler ile İlişkisi

Correlation of FDG PET/CT Parameters with Stage and Pathologic Data in Patients with Non-Small Cell Lung Cancer

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Küçük Hücre Dışı Akciğer Kanserli Hastalarda FDG PET/BT Parametrelerinin Evre ve Patolojik Veriler ile İlişkisi

Özet

Amaç: Akciğer kanserli hastaların pozitron emisyon tomografisi/bilgisayarlı tomografisi (PET/BT) görüntülerinden elde edilen primer lezyonun maksimum standartlaştırılmış alım değeri (SUVmax), SUVmean, metabolik tümör hacmi (MTV) ve total lezyon glikolizi (TLG) değerlerinin hastalık evresi ve patolojik verilerle ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Tıp Fakültesi Nükleer Tıp Anabilim Dalında 2020-2023 tarihleri arasında histopatolojik olarak küçük hücre dışı akciğer kanseri (KHDAK) tanısı alan ve evreleme amacıyla PET/BT görüntülemesi yapılan toplam 81 hasta çalışmaya alındı. Hastaların PET/BT görüntülerinden elde edilen primer lezyonun, SUVmax, SUVmean, MTV ve TLG değerleri ile patolojik veriler not edildi. Küçük hücre dışı akciğer kanseri tanısı alan hastaların PET/BT görüntüleri kullanılarak patolojik veriler eşliğinde TNM evreleme sistemine göre evrelendirildi. Veriler SPSS 20.0 programı ile analiz edildi.

Bulgular: Çalışmaya alınan 66 erkek ve 15 kadın toplam 81 hastanın ortalama yaşı 60±10 (26-78) olarak hesaplanmıştır. Bu çalışmada, KHDAK tanılı hastalar evreleme PET/BT'nin yarı-kantitatif SUVmax, SUVmean, MTV ve TLG değerleri ile ilişkisi analiz edildi. Yaptığımız araştırmaya göre, plevral invazyon, lenf nodu metastazı, tümör çapı ve TNM evre ile SUVmax, SUVmean, MTV ve TLG değerlerinde istatistiksel olarak anlamlı farklılıklar olduğu görüldü($p<0.05$).

Sonuç: Sonuç olarak kısıtlı hasta ile yaptığımız bu çalışmanın SUVmax, SUVmean, MTV ve TLG'nin KHDAK hastalarının sınıflandırılmasında ve tümörün agresifliğinin belirlenmesinde belirgin bir öneme sahiptir. Bu konuda daha geniş kapsamlı prospektif çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Akciğer Kanseri, FDG PET/BT, KHDAK, MTV, TLG.

Abstract

Objective: The aim of this study was to investigate the relationship between the maximum standardized uptake value (SUVmax), SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values of the primary lesion obtained from positron emission tomography/computed tomography (PET/CT) images of lung cancer patients with disease stage and pathological data.

Material and Method: A total of 81 patients with histopathologically diagnosed lung cancer who underwent PET/CT imaging for the diagnosis and staging of lung cancer between 2020 and 2023 in the Department of Nuclear Medicine, Faculty of Medicine, were included in the study. SUVmax, SUVmean, MTV, and TLG values of the primary lesion obtained from PET/CT images of the patients and pathologic data were noted. Patients diagnosed with non-small cell lung cancer (NSCLC) were staged according to the TNM staging system using PET/CT images and pathologic data. Data were analyzed with SPSS 20.0 program.

Results: The mean age of 81 patients, 66 males and 15 females, was 60±10 years (26-78). In this study, we analyzed the association of PET/CT with semi-quantitative SUVmax, SUVmean, MTV, and TLG values in staging patients with NSCLC. According to our study, there were statistically significant differences in SUVmax, SUVmean, MTV, and TLG values with pleural invasion, lymph node metastasis, tumor diameter, and TNM stage ($p<0.05$).

Conclusion: The mean age of 81 patients, 66 males and 15 females, was 60±10 years (26-78). In this study, we analyzed the association of PET/CT with semi-quantitative SUVmax, SUVmean, MTV, and TLG values in staging patients with NSCLC. According to our study, there were statistically significant differences in SUVmax, SUVmean, MTV, and TLG values with pleural invasion, lymph node metastasis, tumor diameter, and TNM stage ($p<0.05$).

Keywords: FDG PET/CT, Lung Cancer, MTV, NSCLC, TLG.

Giriş

Akciğer kanseri, dünya genelinde erkeklerde en yaygın kanser ölüm sebebidir ve kadınlarda bu açıdan ikinci sıradadır. Farklı ülkelerdeki tütün tüketiminin oranına göre, akciğer kanserinin görülme sıklığı popülasyonlar arasında ciddi derecede değişiklik gösterir. Bu, kanserin yayılımının ve etkilerinin coğrafi ve kültürel faktörlere bağlı olarak değiştiğini gösterir (1). Akciğer kanseri genel olarak iki ana türe ayrılır: yaklaşık %80'lik bir orana sahip küçük hücreli dışı akciğer kanseri (KHDAK) ve akciğer kanserlerinin geri kalan %20'sini içeren küçük hücreli akciğer kanseri (KHAK) (2). Akciğer kanserinin erken ve doğru tanısı, başarılı tedavi ve iyi sonuç için çok değerlidir. KHDAK'de evre 1 de tespit edilen hastaların, cerrahi müdahale ile 5 yıllık hayatta kalma oranı yaklaşık olarak %70 civarında olmasına rağmen, metastaz gelişmiş hastalarda, bu durum %5'e kadar düşebilmektedir (2, 3).

Glukoz analogu florodeoksiglukozun (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografisi (PET/BT), görüntülemenin kanserin vücutta yayılımını ve evresini belirlemek, malign/benign ayrımı, nüks ve tedaviye yanıtın saptanması için etkili bir araç olarak görülmekte ve uluslararası kılavuzlarda geniş bir uygulama alanı bulmaktadır (4). Bazı çalışmalarda primer tümörün maksimum standartlaştırılmış alım değeri (SUVmax), KHDAK hastalarında evre, nodal durum, histolojik tip, farklılaşma ve tümör ilerlemesi ile ilişkili olduğu bulunmuştur (5). Bununla beraber FDG-PET/BT ile ölçülen metabolik tümör hacmi (MTV) ve toplam lezyon glikolizi (TLG) gibi hacim parametreleri de maligniteli hastalarda potansiyel prognostik faktörler olarak değerlendirilebilir (6). Yapılan çalışmalarda yüksek MTV ve TLG değerlerinin akciğer kanserinde, genel (OS) ve hastalıksız sağkalım (DFS) için prognostik faktör olarak kullanılabilecekleri ileri sürülmüştür (7). MTV, FDG alımının arttığı tümör dokusunun hacmi olarak tanımlanır. MTV, tüm tümör kütlesinin metabolik bilgisini ifade ettiğinden, tümör özelliklerine, genellikle tümörün yalnızca metabolik olarak en aktif kısmını temsil eden SUV max'a göre daha duyarlı olmasıdır (6). TLG , MTV ve SUVmax parametrelerinin birleşimi olarak, tümör yükünün değerlendirilmesinde kullanılır (8).

Bu çalışmada, retrospektif olarak taranan KHDAK hastalarında TNM evre, lenf nodu metastazı, plevral invazyon, STAS ve Tümör boyutu ile FDG PET/BT'nin yarı-kantitatif SUVmax, SUVmean, MTV ve TLG değerleri arasındaki ilişki analiz edildi.

Gereç ve Yöntem

Çalışma Tasarımı

Çalışmamızda, 2020-2023 yılları arasında Tıp Fakültesi Nükleer Tıp Anabilim Dalına FDG PET/BT için ilk evreleme amacıyla başvuran hastalar arasından belirlenen dahil edilme kriterlerine göre bir çalışma grubu oluşturuldu. Atatürk Üniversitesi Tıp Fakültesi Etik Kurulundan bu çalışma için 16.01.2020 tarihinde 01/48 numaralı karar ile onay alındı.

Çalışmaya hasta dahil edilme kriterleri; patolojik olarak KHDAK tanısı doğrulanmış olmak; daha önceden bilinen başka bir kanser öyküsü olmamak; tetkik öncesinde tümör nedeniyle opere olmamış olmak; tetkik öncesinde tümör nedeniyle kemoterapi (KT) ve radyoterapi (RT) almamış olmak; patoloji raporunda STAS ve plevral invazyona ait verilerin olması olarak belirlendi. Diyabeti olan hastalar (n=2), değerlendirme esnasında görüntü kalitesi tanısal düzeyde olmayan (n=2) ve başka bir primer tümör odağı saptanan hastalar (n=1) çalışma dışı bırakıldı. Çalışmaya dahil edilen hastaların demografik veriler ve patoloji raporuna ait veriler hastane otomasyon sisteminden temin edildi. Hastaların TNM evrelemesi (versiyon 8), FDG PET/BT görüntüleri tek tek yeniden incelenerek Evre I, II, III, IV şeklinde yapıldı.

PET/BT

Hastalar PET/BT için en az 6 saat aç bırakıldı. 18F FDG infüzyonundan önce kan şekeri seviyelerinin 140 mg/dl'den düşük veya buna eşit olduğu doğrulandı. Görüntülemeden 1 saat önce intravenöz olarak 5,5-6,5 MBq/kg 18F FDG uygulandı. Enjeksiyondan bir saat sonra hastanın başından uyluk üst kısmına kadar Biograph 6 PET/BT (Siemens Medical Systems, Almanya) cihazı kullanılarak görüntüsü alındı. Alınan tüm vücut PET/BT görüntüleri nükleer tıp hekimi tarafından patolojik lezyon alanı manuel olarak işaretlendi ve 18F-FDG tutulumuna ait SUVmax, SUVmean, MTV ve TLG değerleri Siemens VIA programı tarafından otomatik olarak ölçülerek kaydedildi. SUVmax eşik değer 2 olarak belirlendi.

Patoloji Verilerinin Elde Edilmesi

STAS; mikropapiller (MP) kümeler, solid yuvalar veya ana tümörün kenarının ötesindeki hava boşluklarında yayılan tek hücreler olarak değerlendirildi. STAS varlığına ve yokluğuna göre olgular 2 guruba ayrıldı. PL0, plevra tutulumu olmayan tümör; PL1, tümör visseral plevranın elastik tabakasının ötesine yayılmış ancak plevral yüzeyde açığa çıkmamış; PL2, plevral yüzeye yayılmış tümör ve PL3, parietal plevraya yayılmış tümör (PL3, pariyetal plevral invazyonla birlikte göğüs duvarı invazyonu olarak sınıflandırılır) olarak değerlendirildi. Plevral invaz olan ve olmayan hastalar 2 gruba ayrıldı.

Tümör boyutu akciğer kanserlerinin evrelemesinde önemli bir faktördür. Primer tümörün boyutuna göre ≤3cm, >3-≤5cm, >5-≤7cm, >7 cm şeklinde 4 gruba ayrıldı.

Lenfovasküler invazyon var /yok şeklinde belirlendi. Patolojik evreleme sonrası vakaların PET/BT görüntüleri ile beraber TNM evrelemeleri yapıldı.

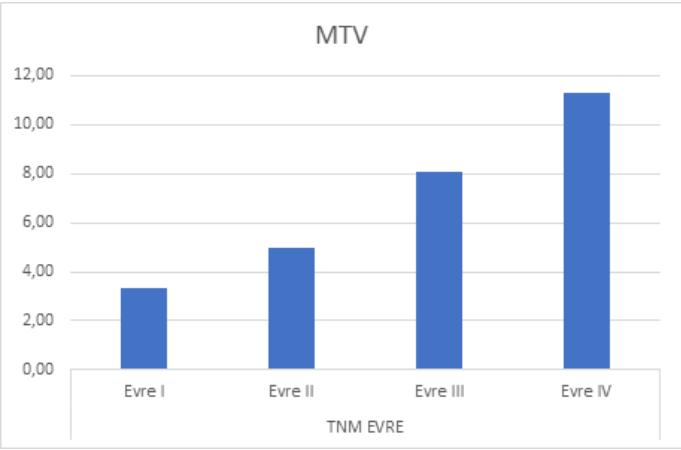
İstatistik Yöntemler

Analizler IBM SPSS 20 istatistik analiz programı ile yapıldı. Veriler ortalama, standart sapma, medyan, minimum, maksimum, yüzde ve sayı olarak sunuldu. Sürekli değişkenlerin normal dağılımına Shapiro Wilk-W testi, Kolmogorov Simirnov testi, Q-Q plot, skewness ve kurtosis ile bakıldı. İki bağımsız grup arasındaki kıyaslamalarda normal dağılım şartı sağlandığı durumda İndependent Samples t testi, sağlanmadığı durumda Mann Whitney u testi kullanıldı. İkiden fazla bağımsız grup ile sürekli değişkenlerin kıyaslanmasında normal dağılım şartı sağlandığı durumda ANOVA testi, sağlanmadığı durumda Kruskal Wallis testi kullanıldı. ANOVA testi sonrası post-hoc testler varyanslar homojen olduğunda Tukey testi ile varyanslar homojen olmadığı durumda Tamhane's T2 testi kullanılarak yapıldı. Kruskal Wallis testi sonrası post-hoc testler için Kruskal Wallis 1-way ANOVA (k samples) testi kullanılarak yapıldı. İki nicel değişkenin kıyaslanmasında normal dağılım şartı sağlanıyorsa Pearson korelasyonu ile sağlanmıyorsa Spearman korelasyon testi kullanıldı. İstatistiksel anlamlılık düzeyi *p<0,05* olarak alındı.

Bulgular

Çalışmamıza 15'i (%18,5) kadın, 66'sı (%81,5) erkek olmak üzere toplam 81 hasta dahil edilmiştir. Hastaların yaş ortalaması 60±10 (min=26, max=78) olarak bulunmuştur. Olguların %29,6'sı (n=24) Evre I, %39,5'i (n=32) Evre II, %18,5'i (n=15) Evre III, %12,3'ü (n=10) Evre IV'dür. Olguların klinik özellikleri Tablo I'de listelenmiştir.

Şekil I. MTV ortalama değerleri ile TNM evreler arasında pozitif bir korelasyon mevcut.



(*r; 0,496 p<0,001*)

Hastaların SUVmax, SUVmean, MTV ve TLG değerleri ile TNM evre arasındaki verilerin istatistiksel analiz sonuçları Tablo II'de verilmiştir. TLG ve MTV değerlerinde Evre I, Evre II, Evre III ile Evre IV arasında istatistiksel olarak anlamlı fark izlendi (*p<0,05*). Ayrıca TLG ve MTV değerlerinde Evre I, Evre II, Evre III ile Evre IV arasında belirgin korelasyon (Şekil I ve II) izlenmiştir. SUVmax ve SUV mean değerleri ile evreler arasında korelasyon olmasına rağmen (Şekil III), yalnızca Evre I-IV ve Evre II-IV arasında istatistiksel olarak anlamlı fark izlendi (*p<0,05*).

Primer tümöre ait SUVmax, SUVmean, MTV ve TLG değerleri bakımından lenf nodu tutulumu olan ve olmayan hastalar arasındaki karşılaştırmalı istatistiksel analiz sonuçları Tablo III'de verilmiştir. Lenf nodu tutulumu olan hastalar ile olmayan hastalar arasında istatistiksel olarak anlamlı farklılıklar gözlenmiştir (*p<0,05*).

Tablo I. Olguların demografik özellikleri

		Sayı	Yüzde
Cinsiyet	Kadın	15	%18,5
	Erkek	66	%81,5
TANI	ADC	45	%55,6
	SCC	36	%44,4
TNM Evre	Evre I	24	%29,6
	Evre II	32	%39,5
	Evre III	15	%18,5
	Evre IV	10	%12,3
Çap (cm)	-≤3	35	%43,2
	>3-≤5	34	%42
	>5-≤7	8	%9,9
	>7	4	%4,9
Lenfovasküler inv.	Var	46	%56,8
	Yok	35	%43,2
Plevral İnv.	Var	25	%30,9
	Yok	56	%69,1
STAS	Var	46	%56,8
	Yok	35	%43,2
Lenf Nodu	Var	22	%27,2
	Yok	59	%72,8

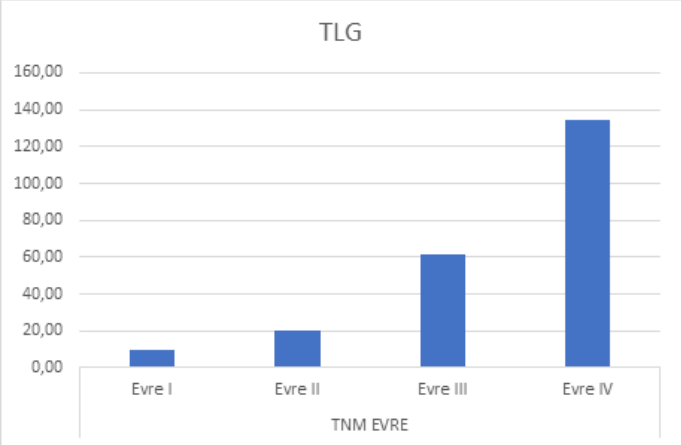
Primer tümöre ait SUVmax, SUVmean, MTV ve TLG değerleri ile plevral invazyon arasındaki ilişkinin istatistiksel analiz sonuçları Tablo IV'te sunulmuştur. Plevral invazyonu olan hastalar ile olmayan hastalar arasında istatistiksel olarak anlamlı farklılıklar gözlemlenmiştir (*p<0,05*).

Tablo II. Hastaların SUVmax, SUVmean, MTV ve TLG değerleri ile TNM Evreleri arasındaki verilerin istatistiksel analiz sonuçları. * Post-hoc teste göre anlamlı olan kategoriler.

TNM	EVRE I	EVRE II	EVRE III	EVRE IV		
	ort ± std	ort ± std	ort ± std	ort ± std	ki-kare	*p*
SUVmax	7,48 ± 7,52*	9,05 ± 6,26	12,73 ± 8,38	18,61 ± 7,38*	19,780	**<0,001**
SUVmean	4,48 ± 4,35*	5,4± 3,65*	7,29± 4,68	10,47± 3,93*	18,555	**<0,001**
TLG	16,15± 18,47*	47,8± 79,41*	119,53± 174,36*	245,48± 236,83*	27,994	**<0,001**
MTV	3,80± 2,92*	7,88± 9,92*	16,29± 21,15*	22,34± 21,07*	20,083	**<0,001**

Primer tümör boyutlarına göre hastalar dört gruba ayrılmıştır: I= ≤3 cm, II= >3-≤5 cm, III= >5-≤7 cm, IV= >7 cm.

Şekil II. TLG ortalama değerleri ile TNM evreler arasında pozitif bir korelasyon mevcut.



(*r; 0,583 p<0,001*)

Hastaların SUVmax, SUVmean, MTV ve TLG değerleri ile lezyon boyutları arasında yapılan istatistiksel analizde, SUVmax ve SUVmean değerlerinde sadece I. ile III. grup arasında anlamlı farklılık saptanmıştır. Benzer şekilde, primer tümörün MTV ve TLG değerleri ile tümör boyutu arasında yapılan analizde, I. ile III.-IV. ve II. ile III.-IV. gruplar arasında anlamlı farklılık bulunmuş (*p<0,05*), ancak I. ile II. ve III. ile IV. grupların kendi arasında anlamlı bir farklılık saptanmamıştır (Tablo V).

Tablo III. Primer tümöre ait SUVmax, SUVmean, MTV ve TLG değerleri ile lenf nodu yayılımı arasındaki verilerin istatistiksel analiz sonuçları.

Lenf nodu metastazı	Var	Yok		
	ort ± std	ort ± std	Z	*p*
SUVmax	15,92±7,96	8,66±7,14	-3,72	**<0,001**
SUVmean	8,99±4,39	5,17±4,11	-3,59	**<0,001**
TLG	161,91±200,19	49,60±105,53	-3,93	**<0,001**
MTV	16,03±17,75	8,12±12,17	-2,73	*0,006*

Patolojik veriler içerisinde STAS ile SUVmax, SUVmean, MTV ve TLG değerleri arasında anlamlı bir ilişki bulunmamıştır (sırasıyla *p=0,303, p=0,263, p=0,469, p=0,610*). Yine patoloji verilerinden lenfovasküler invazyon ile PET-BT parametreleri arasında da anlamlı bir ilişki saptanmamıştır (sırasıyla *p=0,587, p=0,4890, p=0,182, p=0,226*).

Tablo IV. Primer tümöre ait SUVmax, SUVmean, MTV ve TLG değerleri ile plevral invazyon arasındaki verilerin istatistiksel analiz sonuçları.

Plevral inv	Var	Yok		
	ort ± std	ort ± std	Z	*p*
SUVmax	13,89± 8,08	9,50±7,73	-2,382	*0,017*
SUVmean	7,92±4,48	5,60±4,38	-2,328	*0,020*
TLG	155,75±203,87	53,63±108,63	-3,244	*0,001*
MTV	18,90±22,71	7,24±8,01	-2,640	*0,008*

Tartışma

Dünya Sağlık Örgütü'ne (DSÖ) göre akciğer kanseri en sık görülen üç kanserden biridir ve kansere bağlı ölümlerin önde gelen nedenidir (9). Akciğer kanserinin erken ve doğru tanısı, başarılı tedavi ve iyi sonuç için çok değerlidir (10). TNM patolojik evreleme sistemi prognozu belirlemede en çok kabul edilen belirteç olsa da aynı evrede olan hastalardaki farklı prognozu açıklayamamaktadır (11, 12). Bu nedenle kanserin tanı, evreleme ve prognostik değerlendirme için non-invaziv bir yöntem olan PET/BT teknolojisi çok değerlidir (13).

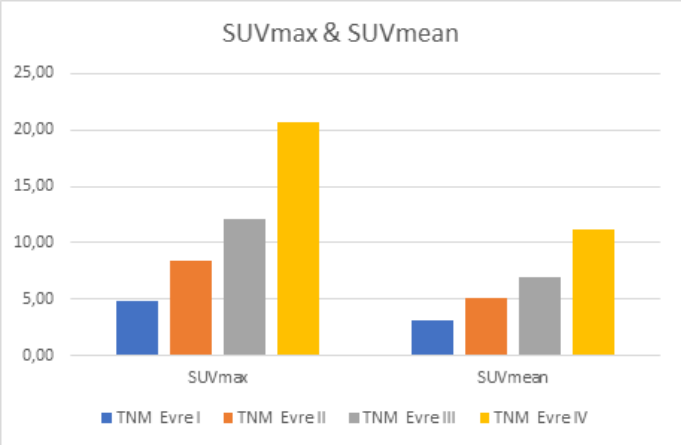
Yaptığımız araştırmaya göre, TNM evre ile primer tümöre ait MTV ve TLG değerlerinde istatistiksel olarak anlamlı bir fark olduğu görüldü. Evreler arttıkça değerlerinde korelatif olarak arttığı izlenmiştir. (Şekil I ve II) Hyun ve arkadaşları 529 erken evre KHDAK hastasının (evre 1 ve 2) çok değişkenli analizinde MTV ile tümör evresi arasında benzer bir ilişki olduğunu göstermiştir (14). Meloni ve arkadaşları (6) erken evre KHDAK hastalarının TLG değerlerinin yüksekliği nüks açısından tümörün daha agresif olduğunu göstermiştir.

Tablo V. Primer tümöre ait SUVmax, SUVmean, MTV ve TLG değerleri ile lezyon çapı arasındaki verilerin istatistiksel analiz sonuçları. [xy] Post-hoc teste göre anlamlı olan kategoriler.

Çap	-≤3cm	>3-≤5cm	>5-≤7cm	>7 cm		
	ort ± std	ort ± std	ort ± std	ort ± std	F	*p*
SUVmax	7,42±6,72[x]	12,14 ±7,85	17,13 ±8,94[x]	12,89 ±8,09	4,724	*0,004*
SUVmean	4,39 ±3,85[x]	7,09 ±4,47	9,06 ±4,17[x]	7,56 ±4,17	4,574	*0,005*
TLG	28,85 ±69,95[x]	54,07 ±48,88[y]	348,93 ±277,86[xy]	212,21 ±216,84[xy]	21,129	*0,000*
MTV	5,83 ±7,46[x]	7,63 ±5,84[y]	35,28 ±29,01[xy]	21,40 ±17,06[xy]	16,851	*0,000*

Chen ve arkadaşları (15) küçük hücreli dışı akciğer kanseri 105 hasta üzerinde yaptıkları çalışmada prognostik tahminde vücut TLG değerinin klinik evrelemede daha iyi bir belirteç olabileceğini tespit etmişler. Bunlara ek olarak Yan ve ark. tarafından yapılan bir çalışmada, primer tümörün MTV'sinin, ileri KHDAK'li hastalarda önemli prognostik faktör olduğunu belirtmişlerdir (16). Yakın zamanlarda yapılan bir araştırmada, çalışmamıza benzer olarak akciğer kanseri hastalarında primer tümörün MTV ve TLG değerlerinin klinik evre ile güçlü bir ilişki içinde olduğu belirtilmiştir. Bu çalışma, bu parametrelerin yüksek seviyelerde olmasının, hastalarda uzak metastaz riskinin artışıyla bağlantılı olduğunu da ortaya koymuştur (17).

Şekil III. SUVmax &SUVmean ortalama değerleri ile TNM evreler arasında pozitif bir korelasyon mevcut.



(SUVmax için *r= 0,473, p<0,001*; SUVmean için *r=0,458, p<0,001*)

Bizim çalışmada SUVmax ve SUVmean değerleri ile TNM evreleme arasında bir korelasyon olduğunu (Şekil III) ancak sadece evre I -IV ve Evre II-IV arasında istatistiksel olarak anlamlı fark olduğunu gördük. Diğer bir değişle Evre I-II, Evre I-III ve Evre III-IV arasında korelasyon olmasına rağmen istatistiksel olarak anlamlı bir sonuç tespit edemedik. Dooms ve arkadaşlarının yapmış olduğu çalışmada (18) primer akciğer tümörlerinde SUVmax ile TNM evreleme arasında bir ilişki bulamadılar. Aslında SUVmax tümör özelliklerinden bağımsız bir dizi değişkenlik faktörüne maruz kaldığından güvenilir bir parametre olmadığına ve bu parametrenin tümör hacmini hesaba katmadığı için tüm tümör lezyonu için metabolik bilgi sağlayamamasından kaynaklandığına dair bilgiler mevcuttur (18, 19). Bu nedenle SUVmax, farklı biyoaktif alanlara sahip birçok akciğer tümörünün heterojenliğini yansıtmaz (6).

Çalışmamızda lezyon boyutları ile PET parametreleri ilişkisinde yaptığımız analizde boyutların grup I, II ve III arasında artan bir korelasyon izlenirken gurup III ile IV arasında korelasyon izlenmemiştir. Bu durum bazı tümörlerin boyut artışı sırasında merkezde nekroza uğraması ile ilişkili olabileceğini düşündürmektedir. Ayrıca birbirine yakın boyutlar arasında istatistiksel olarak belirgin anlamlı farklılık izlenmezken, boyutlar arasındaki fark arttıkça özellikle MTV ve TLG değerlerinde belirgin anlamlı farklılıkların izlendiğini gördük. Literatürde çalışmamızı destekler nitelikte birçok çalışma mevcuttur (20-22).

Plevral invazyonu olan ve olmayan hastalar ile PET parametreleri arasındaki ilişkiye dair literatürde çok çalışma bulunmamakla birlikte, Türe ve arkadaşlarının yapmış olduğu bir çalışmada (23) plevral invazyonu olan hastalarda MTV değerinin diğer parametrelere oranla daha yüksek olduğu izlenmiştir. Çalışmamızda plevral invazyonu olan hastalarda olmayanlara oranla SUVmax, SUVmean, MTV ve TLG değerlerinin istatistiksel olarak daha yüksek olduğu izlendi (*P<0,05*).

Pozitif mediastinal lenf nodlarının KHDAK hastalarında nüks ve ölüm açısından önemli bir prognostik faktör olduğu vurgulanmaktadır (24). Yapılan geniş çaplı birçok çalışmada lenf nodu metastazı olan hastalarda primer tümöre ait PET parametrelerinin daha yüksek olduğu izlenmiştir (25-27). Bizim çalışmamızda da lenf nodu metastazı olan hastalarda olmayanlara göre SUVmax, SUVmean,

TLG ve MTV değerlerinde istatistiksel olarak belirgin artış olduğu izlenmiştir (P<0,05). Bu da SUVmax, SUVmean, TLG ve MTV değerlerinde ki artışın tümörün agresifliğini arttırdığını destekler niteliktedir.

Çalışmamızdaki hasta sayısının göreceli olarak az olması ve her evrede eşit sayıda hasta olmaması çalışmamızın eksikliği olarak düşünülebilir. Her evredeki hasta sayısını eşit tutmak koşuluyla daha geniş çaplı başka çalışmalara ihtiyaç vardır.

Sonuç olarak, tümörün metabolik aktivitesini yansıtan FDG PET/BT görüntüleme yönteminde kullanılan PET parametrelerinin KHDAK sınıflandırılmasında ve tümörün agresifliğinin belirlenmesinde önemli olabileceği görülmüştür.

Teşekkür

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Kaynaklar

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7-30.
2. Abughanimeh O, Kaur A, El Osta B, Ganti AK. Novel targeted therapies for advanced non-small lung cancer. Semin Oncol 2022; 1:S0093-7754(22)00024-0.
3. Wang W, Sun Y, Li H, et al. Surgical modality for stage IA non-small cell lung cancer among the elderly: analysis of the Surveillance, Epidemiology, and End Results database. J Thorac Dis 2020;12(11):6731-6742.
4. Farsad M. FDG PET/CT in the Staging of Lung Cancer. Curr Radiopharm 2020;13(3):195-203.
5. Shimizu K, Maeda A, Yukawa T, et al. Difference in prognostic values of maximal standardized uptake value on fluorodeoxyglucose-positron emission tomography and cyclooxygenase-2 expression between lung adenocarcinoma and squamous cell carcinoma. World J Surg Oncol 2014;12:343.
6. Melloni G, Gajate AM, Sestini S, et al. New positron emission tomography derived parameters as predictive factors for recurrence in resected stage I non-small cell lung cancer. Eur J Surg Oncol 2013;39(11):1254-1261.
7. Christensen TN, Andersen PK, Langer SW, Fischer BMB. Prognostic Value of (18)F-FDG-PET Parameters in Patients with Small Cell Lung Cancer: A Meta-Analysis and Review of Current Literature. Diagnostics (Basel) 2021;11(2):174.
8. Moon SH, Hyun SH, Choi JY. Prognostic significance of volume-based PET parameters in cancer patients. Korean J Radiol 2013;14(1):1-12.
9. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. J Epidemiol Glob Health 2019;9(4):217-222.
10. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2(8):706-714.
11. Birim O, Kappetein AP, van Klaveren RJ, Bogers AJ. Prognostic factors in non-small cell lung cancer surgery. Eur J Surg Oncol 2006;32(1):12-23.
12. Miwa K, Inubushi M, Takeuchi Y, et al. Performance characteristics of a novel clustered multi-pinhole technology for simultaneous high-resolution SPECT/PET. Ann Nucl Med 2015;29(5):460-466.
13. Sun Y, Xiao L, Wang Y, et al. Diagnostic value of dynamic (18)F-FDG PET/CT imaging in non-small cell lung cancer and FDG hypermetabolic lymph nodes. Quant Imaging Med Surg 2023;13(4):2556-2567.
14. Hyun SH, Choi JY, Kim K, et al. Volume-Based Parameters of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Improve Outcome Prediction in Early-Stage Non–Small Cell Lung Cancer After Surgical Resection. Annals of Surgery 2013;257(2):364-370.
15. Chen HHW, Chiu N-T, Su W-C, Guo H-R, Lee B-F. Prognostic Value of Whole-Body Total Lesion Glycolysis at Pretreatment FDG PET/CT in Non–Small Cell Lung Cancer. Radiology 2012;264(2):559-566.
16. Yan H, Wang R, Zhao F, et al. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced non-small cell lung cancer treated by non-surgical therapy. Acta Radiologica 2011;52(6):646-650.
17. Hu WD, Wang HC, Wang YB, Cui LL, Chen XH. Correlation study on 18F-FDG PET/CT metabolic characteristics of primary lesion with clinical stage in lung cancer. Q J Nucl Med Mol Imaging 2021;65(2):172-177.
18. Dooms C, Vansteenkiste J. Prognostic Value of Fluorodeoxyglucose Uptake in Non-small Cell Lung Cancer: Time for Standardization and Validation. J Thorac Oncol 2010;5(5):583-584.
19. Cazaentre T, Morschhauser F, Vermandel M, et al. Pre-therapy 18F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapy in non-Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37(3):494-504.
20. Sahiner I, Atasever T, Akdemir UO, Ozturk C, Memis L. Relationship between primary lesion metabolic parameters and clinical stage in lung cancer. Rev Esp Med Nucl Imagen Mol 2013;32(6):357-363.
21. Li M, Liu N, Hu M, et al. Relationship between primary tumor fluorodeoxyglucose uptake and nodal or distant metastases at presentation in T1 stage non-

small cell lung cancer. Lung Cancer 2009;63(3):383-386.
22. Erol M, Önner H, Taştekin G. Akciğer Kanserli Hastalarda F-18 FDG PET/BT Parametrelerinin Klinik Evre ile İlişkisi. Selcuk Tip Dergisi 2021;1(37):24-31.
23. Türe E, Özmen Ö, Kabalak P, Demiröz Ş, Uğurman F. Opere Küçük Hücreli Dişi Akciğer Kanseri Olgularinda PET-BT'de Ölçülen Volümetrik Parametrelerin Post-Operatif Rekürrens Üzerine Etkisi. TÜSAD Solunum 2021; Ankara, Türkiye2021. p. 128.
24. Lebioda A, Makarewicz R, Malkowski B, Dancewicz M, Kowalewski J, Windorbska W. Measurement of primary tumor volume by PET-CT to evaluate risk of mediastinal nodal involvement in NSCLC patients with clinically negative N2 lymph nodes. Rep Pract Oncol Radiother 2013;18(2):76-81.
25. Park SY, Yoon JK, Park KJ, Lee SJ. Prediction of occult lymph node metastasis using volume-based PET parameters in small-sized peripheral non-small cell lung cancer. Cancer Imaging 2015;15:21.
26. Kim DH, Song BI, Hong CM, et al. Metabolic parameters using (1)(8)F-FDG PET/CT correlate with occult lymph node metastasis in squamous cell lung carcinoma. Eur J Nucl Med Mol Imaging 2014;41(11):2051-2057.
27. Chang C, Sun X, Zhao W, et al. Minor components of micropapillary and solid subtypes in lung invasive adenocarcinoma (</= 3 cm): PET/CT findings and correlations with lymph node metastasis. Radiol Med 2020;125(3):257-264.

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The Effect of Albumin to Alkaline Phosphatase Ratio on Survival in Patients with Metastatic Bone Sarcomas

Metastatik Kemik Sarkomlu Hastalarda Albumin-Alkalen Fosfataz Oranının Sağ Kalıma Etkisi

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The Effect of Albumin to Alkaline Phosphatase Ratio on Survival in Patients with Metastatic Bone Sarcomas

Abstract

Objective: To investigate the effect of albumin to alkaline phosphatase ratio (AALPR) on survival in patients with metastatic bone sarcomas.

Patients and Method: 60 patients with metastatic bone sarcomas were included in the study. The relationship between AALPR before chemotherapy and overall survival (OS) and progression free survival (PFS) was evaluated with Cox regression multivariate analysis.

Results: Of the patients in the study, 25 (58.3%) were osteosarcoma, 16 (26.7%) Ewing's sarcoma, 5 (8.3%) chondrosarcoma and 4 (6.7%) giant cell bone tumor. AALPR was 0.039 obtained in ROC analysis. The median PFS and OS at AALPR ≥ 0.039 group were statistically significantly higher than the group with <0.039 (*p=0.006, p=0.003*). AALPR <0.039 was found to be associated with poor OS and PFS (OS, HR=1.778, 95% CI, 1.211-1.912, *p=0.023* - PFS, HR=4.782, 95% CI, 1.963-11,647, *p=0.001*).

Conclusion: In our study, low AALPR value before chemotherapy was associated with poor OS and PFS in patients with metastatic bone sarcoma. Low AALPR has been associated with poor OS and PFS in many cancer types, but the association of AALPR with survival at bone sarcoma patients has not been evaluated previously. Our study is the first in the literature to investigate this issue. AALPR can be used as an inexpensive and simple marker to evaluate the prognosis of patients. However, studies with larger number of patients are needed to give more precise results.

Keywords: Albumin-to-alkaline phosphatase ratio, bone cancer, neutrophil to lymphocyte ratio, osteosarcoma.

Özet

Amaç: Metastatik kemik sarkomu hastalarında albümin-alkalen fosfataz oranının (AALPO) sağ kalıma etkisini araştırmak.

Hastalar ve Yöntem: Çalışmaya metastatik evrede olan 60 kemik sarkomu hastası dahil edildi. Kemoterapi öncesi bakılan AALPO ile genel sağkalım (GS) ve progresyonsuz sağkalım (PS) arasındaki ilişki Cox regresyonu multivariate analizi ile değerlendirildi.

Bulgular: Çalışmaya alınan hastaların 25 (%58,3)'i osteosarkom, 16 (%26,7)'si Ewing sarkomu, 5 (%8,3)'ü kondrosarkom ve 4 (%6,7)'ü dev hücreli kemik tümörüydü. ROC analizi ile elde edilen AALPO değeri 0,039 olarak bulundu. AALPO ≥ 0,039 grubundaki medyan PS ve GS, <0,039 olan gruba göre istatistiksel olarak anlamlı derecede yüksekti (*p=0,006, p=0,003*). AALPO <0,039 (HR=1,778, %95 CI, 1,211-1,912, *p=0,023*) olması düşük genel GS ile ilişkili ve (HR=4,782, %95 CI, 1,963-11,647, *p=0,001*) olması düşük PS ile ilişkili bulundu.

Sonuç: Çalışmamızda metastatik kemik sarkomlu hastalarda kemoterapi öncesi düşük AALPO değeri, kötü GS ve PS ile ilişkili bulunmuştur. Daha önce birçok kanser türünde düşük AALPO kötü GS ve PS ile ilişkili bulunmuştur ancak daha önce kemik kanseri hastalarında AALPO'nun sağ kalım ile ilişkisi değerlendirilmemiştir. Çalışmamız literatürde bu konuyu araştıran ilk çalışmadır. AALPO, hastaların prognozunu değerlendirmede ucuz ve basit bir belirteç olarak kullanılabilir. Ancak daha kesin sonuçlar söylemek için daha fazla hasta sayısı ile yapılacak çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Albumin alkalen fosfataz oranı, kemik kanseri, nötrofil lenfosit oranı, osteosarkom.

Introduction

Sarcomas are types of cancer that arise from the connective tissue of the body. They are named according to the tissue they originate as bone sarcoma or soft tissue sarcoma. Bone sarcomas have subtypes of osteosarcoma, chondrosarcoma, Ewing's sarcoma, and giant cell bone tumor. The most common of these is osteosarcoma, which originates from osteoclast cells. Ewing's sarcoma originating from bone marrow or primitive neuroectodermal cells is the second most common bone cancer (1). Chondrosarcoma and giant cell bone tumors are much less common types. Osteosarcomas often arise from the long bones such as the tibia, humerus, femur. Ewing's sarcoma and giant cell bone tumors are common in the diaphysis of flat bones, such as the pelvis, scapula, as well as long bones (2). Chondrosarcoma is more common in vertebrae. The most common distant metastase sites of all bone tumors are the lungs. The probability of metastasis of giant cell tumors of the bone is very low compared to other bone tumors, and the most common site of distant metastasis is the lungs (3). Although bone cancers are rarely seen all over the world, mortality and morbidity rates are high. The 5-year overall survival rate for metastatic bone cancers is approximately 30% (4).

The increase in cancer cases and the variety of treatments have brought about the search for more easily applicable, inexpensive and practical biomarkers. The development of practical markers to predict the prognosis of patients before treatment is necessary for better treatment responses. As an indicator of liver function tests, albumin is the most abundant protein in plasma and its plasma level reflects the function of organs. Albumin is a biomarker used in cancer and non-cancer (liver diseases, nutritional status, diabetes mellitus, etc.) diseases (5). Elevated alkaline phosphatase (ALP) is a marker used primarily in skeletal system, hepatobiliary system, and cardiovascular system diseases. As in albumin, elevated ALP can be observed in benign (cholestasis, bone fracture, etc.) and malignant (bone cancers, pancreatic cancer, etc.) conditions. Elevated ALP in malignant conditions is associated with poor prognosis (6). Albumin to ALP ratio (AALPR) was first investigated in patients with hepatocellular cancer (HCC). Later, it was also investigated in breast cancer, nasopharyngeal cancer, non-small cell lung cancer, genitourinary system cancers and low AALPR was associated with shorter survival (7).

In our study, we aimed to investigate the survival effect of AALPR, which was performed before metastatic first-line chemotherapy, in bone sarcomas patients with distant metastases.

Material and Method

The study was carried out with the permission of the Erciyes University Scientific Research Evaluation and Ethics Committee (Date: 22.09.2022 Decision No: 2022/675). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In the study, the clinical, laboratory, radiological and demographic characteristics of cancer patients who were diagnosed with metastatic bone sarcoma by pathological and radiological tests and followed up in the medical oncology clinic of Erciyes University between January 2008 and April 2022 were evaluated retrospectively. 60 patients were included in the study. Inclusion criteria for the study; to be between the ages of 18-85, to have osteosarcoma, Ewing's sarcoma, chondrosarcoma or giant cell bone cancer diagnoses, to be in the metastatic stage at the time of diagnosis or during follow-up, to have received chemotherapy treatment for at least 3 months in the metastatic stage. The exclusion criteria are; being younger than 18 years old, having the current stage of the disease as a local disease or locally advanced stage, having received chemotherapy for less than 3 months and having hepato-biliary disease. The information of the patients was scanned retrospectively from the files of the oncology clinic and the hospital database. Clinicopathological features, whole blood and plasma biochemistry parameters of the patients were recorded.

Statistical Analysis

AALPR; with the formula albumin (g/dL) / ALP (u/L), neutrophil to lymphocyte ratio (NLR); with neutrophil (10^3/µL) / lymphocyte (10^3/µL) formula, platelet to lymphocyte ratio (PLR); calculated with the platelet (10^3/µL) / lymphocyte (10^3/µL) formula. ROC analysis was performed for optimal AALPR, NLR, and PLR cut-off values with high sensitivity and specificity and patients were categorized according to this value. The normality distribution for continuous variables was evaluated with the Kolmogorov test. The Mann-Whitney U test was used for comparative analysis between two independent groups in data that did not fit the normal distribution. Numerical and categorical variables were compared with the independent sample T test in data with normal distribution. Significance between the categorized groups was evaluated with the chi-square test. Differences in overall survival (OS) and progression-free survival (PFS) between categorized groups were evaluated using log rank curves and Kaplan-Meier test. Multivariate analysis was performed on the statistically significant data with Cox regression analysis. Analysis results were

presented as median (minimum-maximum), mean, standard deviation, and hazard ratio (HR). *p<0.05* was considered statistically significant in all statistical tests performed at the 95% confidence interval (CI). For data that could be clinically significant, *p<0.200* was also included in the multivariate analysis.

Results

Median age was 24 (18-70) years in the whole group. 58.3% of the patients had osteosarcoma. 43.3% of the patients were initially at the metastatic stage. The most common localization site was the upper extremity with a rate of 40%. 36.7% of the patients received adjuvant/neoadjuvant chemotherapy and 15% adjuvant/neoadjuvant radiotherapy. Partial response (PR) and complete response (CR) were 40% and 6.7% respectively in patients with metastatic first-line chemotherapy. ROC analysis was performed for AALPR, NLR, and PLR values."Area under the ROC Curve (AUC)" value obtained for AALPR, NLR, and PLR was statistically significant(AUC=0.795, AUC=0.657, AUC=0.648).

The "cut-off" values obtained for all three parameters as a result of the analyses were examined. AALPR ≥ 0.039 was better predictive for survival than the other two parameters. (sensitivity =72.1%, specificity =79.4%). Patients were grouped to AALPR <0.039 (A) and ≥ 0.039 (B). Groups A and B were compared with the X^2 test. Significant differences were observed between the two groups in terms of histology, progression status under chemotherapy, ALP, and albumin values. Median ALP values were

Table I. Comparison of clinical characteristic sand laboratory parameters according to the AALPR cut-off value

Variables	Categories	AALPR<0.039 (n=30) (A)	AALPR ≥ 0.039 (n=30) (B)	Total (n=60)	*p- value*
Age (median/ min-max)		22 (18-60)	23 (18-70)	24 (18-70)	*0.059* [1]
Gender, n (%)	Male	14 (46.7%)	20 (66.7%)	34 (56.7%)	*0.118* [2]
	Female	16 (53.3%)	10 (33.3%)	26 (43.3%)	
Histology, n (%)	Osteosarcoma	22 (73.3%)	13 (43.3%)	35 (58.3%)	***0.022***
	Chondrosarcoma	1 (3.3%)	4 (13.3%)	5 (8.3%)	
	Ewing sarcoma	4 (13.3%)	12 (40%)	16 (26.7%)	
	Giant cell bone tumor	3 (10%)	1 (3.3%)	4 (6.7%)	
Adjuvant/ neoadjuvant chemotherapy, n (%)	Yes	10 (333%)	12 (40%)	22 (36.7%)	*0.592*
	No	20 (66.7%)	18 (63.3%)	38 (63.3%)	
Adjuvant/ neoadjuvant radiotherapy, n (%)	Yes	5 (16.7%)	4 (13.3%)	9 (15%)	*0.717*[3]
	No	25 (83.3%)	26 (86.7%)	51 (85%)	
Progression status under chemotherapy, n (%)	Yes	23 (76.7%)	15 (50%)	38 (63.3%)	***0.032***
	No	7 (23.3%)	15 (50%)	22 (36.7%)	
Exitus status, n (%)	Yes	22 (73.3%)	16 (53.3%)	38 (63.3%)	*0.108*
	No	8 (26.7%)	14 (46.7%)	22 (36.7%)	
PLR (mean)		0.218±0.110	0.201±0.079	0.209±0.095	*0.494* [4]
NLR (median/ min-max)		3.875 (1.772-11.912)	2.972 (0.942-13.393)	3.426 (0.942-13.393)	*0.169* [3]
ALP (U/L) (median/ min-max)		150 (82-4429)	83 (48-163)	110 (48-4429)	***<0.001*** [3]
Albumin (g/dL) (median/ min-max)		4 (2.140-5.100)	4.285 (3-5.310)	4.075 (2.140-5.310)	***0.007*** [3]
LDH (U/L) (median/ min-max)		268 (153-937)	229 (123-1051)	259 (123-1051)	*0.067* [3]
NLR, n (%)	<3.154	11 (36.7%)	17 (56.7%)	28 (46.7%)	*0.121*
	≥ 3.154	19 (63.3%)	13 (43.3%)	32 (53.3%)	
PLR, n (%)	<0.191	13 (43.3%)	16 (53.3%)	29 (48.3%)	*0.438*
	≥ 0.191	17 (56.7%)	14 (46.7%)	31 (51.7%)	

[1]Mann-Whitney U test, [2]Chi-squared test, [3]Fisher exact test, [4]Independent sample T test AALPR: Albumin alkaline phosphatase ratio, NLR:Neutrophil lymphocyte ratio, PLR:Platelet lymphocyte ratio, LDH:Lactatede hydrogenase, PR:Partial response, CR: Complete response, SD:Stable disease, PD:Progressive disease

significantly higher in group A and median albumin values was significantly higher in group B (*p<0.001, p=0.007* respectively) (Table I).

The median OS was 47 months. There was no statistically significant OS difference in terms of age, gender, tumor localization, adjuvant/neoadjuvant chemotherapy-radiotherapy status, NLR groups, and PLR groups. Median OS was 153 months in the chondrosarcoma group and it was statistically significantly higher than in other histologies (*p=0.005*). Median OS was 47 months with AALPR ≥ 0.039 and it was statistically significantly higher than with <0.039 (*p=0.003*).

The median PFS was 15 months. There was no difference in PFS in terms of age, gender, surgery status, tumor localization, adjuvant/neoadjuvant

Table II. Comparison of the OS and PFS times according to the characteristics of the patients.

Variables	Categories	Median OS (Month) 95% CI (Min-Max)	*p-value**	Median PFS (Month) 95% CI (Min-Max)	*p- value* *
Survival	General population	47 (35.703-58.297)		15 (10.688-19.312)	
Age	<45	46 (36.583-55.417)	*0.963*	14 (9.460-18.540)	*0.71*
	≥45	49 (36.124-62.353)		20 (13.099-26.901)	
Gender	Male	46 (33.48-55.519)	*0.680*	14 (10.958-17.015)	*0.86*
	Female	49 (39.544-68.456)		17 (11.578-22.422)	
Histology	Osteosarcoma	47 (34.586-59.414)	***0.005***	14 (4.489-23.511)	***0.048***
	Chondrosarcoma	153 (152.040-155.960)		37 (13.119-82.061)	
	Ewing sarcoma	25 (16.629-33.371)		13 (8.497-17.503)	
	Giant cell bone tumor	121 (119-121)		120 (110.235-121)	
Initialstage	Local/resectable	102 (72.965-131.570)	***<0.001***	81 (56.968-105.698)	***0.02***
	Local advanced/unresectable	58 (59.094-111.550)		35 (12.061-58.302)	
	Metastatic	22 (14.658-29.342)		20 (10.220-30.099)	
Surgery	Yes	90 (69.863-11.968)	***<0.001***	17 (11.365-39.860)	*0.077*
	No	29 (18.586-40.537)		13 (9.951-16.049)	
Localization	Lower extremity	35 (25.168-44.832)	*0.601*	12 (7.845-16.155)	*0.235*
	Upper extremity	47 (26.513-67.487)		18 (6.586-29.414)	
	Trunk-pelvis	63 (22.587-103.413)		42 (12.124-88.192)	
	Head and neck	49 (45.799-52.201)		17 (8.998-25.002)	
Adjuvant/neoadjuvant chemotherapy	Yes	66 (10.254-144.873)	*0.342*	17 (5.558-21.569)	*0.296*
	No	38 (10.536-47.464)		13 (7.546-18.454)	
Adjuvant/neoadjuvant radiotherapy	Yes	58 (48.770-217.230)	*0.420*	37 (3.773-70.227)	*0.702*
	No	38 (22.712-53.288)		15 (10.334-19.666)	
First line chemotherapy response	CR	143 (123.400-162.600)	***<0.001***	37 (1.793-72.207)	***<0.001***
	PR	99 (73.425-124.844)		30 (8.941-39.156)	
	SD	47 (33.938-61.462)		18 (10.531-25.469)	
	PD	14 (6.524-21.476)		6 (4.889-7.111)	
NLR	<3.154	49 (12.719-85.281)	*0.138*	17 (10.100-23.900)	*0.491*
	≥ 3.154	46 (25.667-66.333)		14 (10.291-17.709)	
PLR	<0.191	39 (16.035-61.965)	*0.900*	14 (4.988-23.012)	*0.787*
	≥ 0.191	47 (45.418-48.582)		15 (10.356-19.644)	
AALPR	<0.039	39 (26.046-51.954)	***0.003***	9 (2.982-15.018)	***0.006***
	≥ 0.039	47 (42.126-69.547)		24 (16.979-31.021)	

OS: Overall survival, PFS: Progression free survival, Min: Minimum, Max: Maximum, AALPR: Albumin alkaline phosphatase ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LDH: Lactate dehydrogenase , PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease

chemotherapy-radiotherapy status, NLR groups, and PLR groups. The median PFS in the chondrosarcoma group was 37 months and it was statistically significantly higher than other histologies (*p=0.048*). Median PFS was 24 months with AALPR ≥ 0.039 and it was statistically significantly higher than with <0.039 (*p=0.006*) (Table II).

Table III. Cox regression analysis results of the OS and PFS

		Multivariate OS *		Multivariate PFS *	
Variables	**Categories**	**HR (95% CI) (Min-Max)**	***p-value***	**HR (95% CI) (Min-Max)**	***p- value***
Histology	Giant cell bone tumor (ref)		*0.073*		*0.778*
	Osteosarcoma	20.443 (2.162-193.288)	*0.008*	17.012 (0.257-35.265)	*0.891*
	Chondrosarcoma	12.312 (3.568-125.147)	*0.957*	13.568 (0.895-57.865)	*0.898*
	Ewing sarcoma	19.112 (1.810-201.832)	*0.014*	15.745 (0.658-95.145)	*0.895*
Initial stage	Local/resectable (ref)		***0.036***		*0.223*
	Local advanced/unresectable	2.222 (0.589-8.386)	*0.239*	1.256 (0.176-9.388)	*0.086*
	Metastatic	17.492 (1.981-154.428)	*0.010*	2.865 (0.054-3.283)	*0.804*
Surgery	Yes (ref)	0.667 (0.095-4.673)	*0.684*		
First line chemotherapy response	CR (ref)		*0.115*		*0.526*
	PR	0.189 (0.024-1.484)	*0.113*	0.254 (0.029-2.260)	*0.219*
	SD	1.158 (0.144-9.277)	*0.890*	1.480 (0.178-12.332)	*0.452*
	PD	4.107 (0.557-30.303)	*0.166*	3.149 (0.034-2.580)	*0.717*
NLR	<3.154 (ref)	1.320 (1.012-2.803)	***0.032***		
AALPR	≥ 0.039 (ref)	1.778 (1.211-1.912)	***0.023***	4.782 (1.963-11.647)	***0.001***

*Risk factors affecting OS and PFS were analysed by Cox regression analysis as multivariate models. OS: Overall survival, PFS:Progression free survival, Min:Minimum, Max: Maximum, HR:Hazard ratio, AALPR:Albumin alkaline phosphatase ratio, NLR:Neutrophil lymphocyte ratio, PR:Partial response, CR: Complete response, SD:Stable disease, PD:Progressive disease

Cox regression multivariate analysis was performed using log rank curves and the Kaplan Meier test variables with significant differences between the groups in terms of OS and PFS, and the NLR variable that was considered clinically significant. Being metastatic at diagnosis (HR=17.492, 95% CI, 1.981-154.428, *p=0.010*), NLR≥3.154 (HR= 1.320, 95%CI, 1.012-2.803, *p=0.032*) and AALPR <0.039 (HR=1.778, 95% CI, 1.211-1.912, *p=0.023*) was found to be associated with poor OS. AALPR <0.039 (HR=4.782, 95% CI, 1.963-11.647, *p=0.001*) was associated with poor PFS (Table III).

Discussion

Bone sarcomas are a rare type of cancer and therefore there are still deficiencies in prognostic markers. NLR has previously been investigated to determine prognosis in bone sarcomas patients and similar results were found in this study as well as in other studies. The association of higher NLR with worse survival was previously demonstrated in solid tumors. The correlation between higher NLR values and worse survival in osteosarcoma patients in the literature was found to be statistically significant (OS, HR= 2.097, 95% CI, 1.202–3.658, *p=0.009*) (8). In another study, high NLR before treatment was associated with poor survival in nonmetastatic osteosarcoma patients (OS, HR= 1.810, 95% CI, 1.23–2.67, *p=0.003*) (9). In another study involving patients with chondrosarcoma, osteosarcoma, and Ewing's sarcoma, high NLR levels were found to be associated with worse survival (OS, HR= 2.200, 95% CI, 1.000-5.200, *p=0.003*) (10. In our study, high NLR was associated with poor survival, consistent with the literature (HR= 1.320, 95% CI, 1.012-2.803, *p=0.032*). PLR has also been previously investigated for prognosis in bone sarcoma patients, and high PLR values have been associated with poor survival. However, no statistically significant relationship was found in our study, possibly due to the small number of patients.

In the study, we demonstrated for the first time the prognostic value of AALPR in bone sarcoma patients. AALPR was first investigated in HCC patients, and the effect of AALPR on prognosis and survival in various cancers has continued to be investigated thereafter. Chan AW. et al. found low AALPR to be an independent prognostic factor for poor survival in HCC patients (OS, HR= 2.357, 95% CI, 1.354–4.102, *p=0.002*- PFS, HR=1.852, 95% CI, 1.158–2.964, *p=0.010*) (11). Later, Nie M. et al. found that low AALPR is an independent prognostic factor for worse survival in patients with metastatic nasopharyngeal

cancer (HR=2.295, 95% CI, 1.217-4.331, *p=0.042*) (12). On the other hand, in the studies of Zeng X. et al. (OS, HR= 1.570, 95% CI, 0.670-3.720, *p=0.300*- PFS, HR=1.980, 95% CI, 0.940-4.140, *p=0.070*) and Kim JS. et al. (OS, HR= 0.566, 95% CI, 0.236-1.356, *p=0.202*- PFS, HR=0.715, 95% CI, 0.322-1.587, *p=0.410*) at locally advanced nasopharyngeal cancer patients, no statistically significant relationship was found between AALPR and survival. However, it was significant in the analysis in which all stages were included (13,14). In a study by Li D. et al. at patients with metastatic non-small cell lung cancer, higher AALPR was associated with good survival (OS, HR= 0.657, 95% CI, 0.504–0.856, *p=0.002*) (15). Xiong JP et al. at operable cholangiocellular cancer patients (OS, HR=2.880, 95% CI, 1.190-5.780, *p=0.002*- PFS, HR=2.310, 95% CI, 1.40–3.29, *p<0.001*) and Pu N et al. at operable pancreatic cancer patients (OS, HR=2.086, 95% CI, 1.272-3.423, *p=0.004*) demonstrated that lower preoperative AALPR was associated with worse survival (16,17). Higher preoperative AALPR was associated with better survival in patients who subsequently underwent surgery for cervical cancer (OS, HR= 0.331, 95% CI, 0.135-0.809, *p=0.015*- PFS, HR=0.387, 95% CI, 0.176-0.853, *p=0.019*) (18). As seen in the literature, AALPR has been previously investigated in different cancer types and generally low AALPR is associated with poor survival. However, the effect of AALPR on prognosis in bone sarcoma has not been investigated before. We investigated the effect of AALPR on bone sarcoma prognosis for the first time. Similar to other cancer types, we found low AALPR to be associated with worse survival in bone sarcomas (OS, HR=1.778, 95% CI, 1.211-1.912, *p=0.023*-PFS, HR=4.782, 95% CI, 1.963-11.647, *p=0.001*).

Our study is the first in the literature to show the association of low AALPR with poor survival in patients with bone sarcomas. However, this study has several limitations. Firstly, this study is retrospective. Second, despite their advantage in this cohort, the markers were a nonspecific predictor for bone sarcomas and thus inevitably had inherent weaknesses and limitations. However, there is no specific serum marker for bone sarcomas. The most important limitation of our study was that it was a single-center, retrospective study, and the number of patients was limited.

Conclusion

In our study, low AALPR value before chemotherapy was associated with poor OS and PFS in patients with metastatic bone sarcoma. Low AALPR has been associated with poor OS and PFS in many cancer types, but the association of AALPR with survival at bone sarcoma patients has not been evaluated previously. Our study is the first in the literature to investigate this issue. AALPR evaluation before chemotherapy can be used as a cheap and simple marker that can give an idea about the prognosis and survival of patients with metastatic bone sarcomas diagnosis. However, larger studies with larger number of patients are needed for this.

References

1. Rizk VT, Walko CM, Brohl AS. Precision medicine approaches for the management of Ewing sarcoma: current perspectives. *Pharmacogenomics and Personalized Medicine* 2019;12:9.
2. Atrayee BM, Chawla SP. Giant Cell Tumor of Bone: An Update. *Current Oncology Reports* 2021;23(5):51
3. Hashimoto K, Nishimura S, Oka N, Akagi M. Clinical features and outcomes of primary bone and soft tissue sarcomas in adolescents and young adults. *Molecular and clinical oncology* 2020;12(4):358-364.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: a cancer journal for clinicians* 2019;69(1):7-34.
5. Jagdish RK, Maras JS, Sarin SK. Albumin in advanced liver diseases: The good and bad of a drug! *Hepatology* 2021;74(5):2848-2862.
6. Siller AF, Whyte MP. Alkaline phosphatase: discovery and naming of our favorite enzyme. *Journal of Bone and Mineral Research* 2018;33(2):362-364.
7. An L, Yin W-t, Sun D-w. Albumin-to-alkaline phosphatase ratio as a promising indicator of prognosis in human cancers: is it possible? *BMC cancer* 2021;21(1):1-18.
8. Li W, Luo X, Liu Z, Chen Y, Li ZJPo. Prognostic value of C-reactive protein levels in patients with bone neoplasms: a meta-analysis. PLoS One 2018;13(4):e0195769.
9. Li Y-J, Yao K, Lu M-X, Zhang W-B, Xiao C, Tu C-Q. Prognostic value of the C-reactive protein to albumin ratio: a novel inflammation-based prognostic indicator in osteosarcoma. *OncoTargets and therapy* 2017;10:5255.
10. Xin S, Wei G. Prognostic factors in osteosarcoma: A study level meta-analysis and systematic review of current practice. J Bone Oncol 2020;21:100281.
11. Zhang X, Xin Y, Chen Y, Zhou XJSR. Prognostic effect of albumin-to-alkaline phosphatase ratio on patients with hepatocellular carcinoma: a systematic review and meta-analysis. Sci Rep 2023;13(1):1808.
12. Nie M, Sun P, Chen C, et al. Albumin-to-alkaline phosphatase ratio: a novel prognostic index of overall survival in cisplatin-based chemotherapy-treated

patients with metastatic nasopharyngeal carcinoma. *Journal of Cancer* 2017;8(5):809.
13. Kim JS, Keam B, Heo DS, et al. The prognostic value of albumin-to-alkaline phosphatase ratio before radical radiotherapy in patients with non-metastatic nasopharyngeal carcinoma: a propensity score matching analysis. *Cancer research and treatment: official journal of Korean Cancer Association* 2019;51(4):1313-1323.
14. Zeng X, Liu G, Pan Y, Li Y. Prognostic value of clinical biochemistry-based indexes in nasopharyngeal carcinoma. *Frontiers in oncology* 2020;10:146.
15. Li D, Yu H, Li W. Albumin-to-alkaline phosphatase ratio at diagnosis predicts survival in patients with metastatic non-small-cell lung cancer. *OncoTargets and therapy* 2019;12:5241.
16. Strijker M, Chen J, Mungroop T, et al. Systematic review of clinical prediction models for survival after surgery for resectable pancreatic cancer. Br J Surg 2019;106(4):342-354.
17. Xiong J-P, Long J-Y, Xu W-Y, et al. Albumin-to-alkaline phosphatase ratio: a novel prognostic index of overall survival in cholangiocarcinoma patients after surgery. World J Gastrointest Oncol 2019;11(1):39.
18. Zhang C, Li Y, Ji R, et al. The prognostic significance of pretreatment albumin/alkaline phosphatase ratio in patients with stage IB-IIA cervical Cancer. *OncoTargets and therapy* 2019;12:9559.

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Atherogenic index of plasma as a Novel Biomarker to Predict Retinal Vein Occlusion

Retinal Ven Tıkanıklığı Risk Belirteci Olarak Aterojenik Plazma İndeksi

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Atherogenic index of plasma as a Novel Biomarker to Predict Retinal Vein Occlusion

Abstract

Objective: Atherogenic index of plasma is a relatively new index used to predict the risk of cardiovascular diseases in the general population. Our aim was to investigate association between the development of retinal vein occlusion and atherogenic index of plasma.

Material and Method: A total of 24 patients with retinal vein occlusion and 24 age-sex matched healthy individuals were included in this retrospective study. The demographic characteristics and laboratory findings of the patients and control subjects were obtained from the electronic medical records. Atherogenic index of plasma was calculated as the logarithmical ratio of molar concentrations of triglycerides to high density lipoprotein cholesterol as. The association among atherogenic index of plasma, lipid metabolism parameters, and retinal vein occlusion was analyzed.

Results: The median age was 69.5 (range, 48-86) in the patient group and 71.5 (range, 50-84) in the control group ($p=812$). Although there were no significant differences in terms of total cholesterol and low-density lipoprotein cholesterol between two groups ($p=0.458, 0.88$), atherogenic index of plasma was significantly higher in the patient group ($p<0.05$).

Conclusion: Elevated atherogenic index of plasma values might aid clinicians raise suspicion against a possible retinal vein occlusion attack and take precautions accordingly to prevent complications related to retinal vein occlusion.

Keywords: Atherogenic index of plasma, lipid profile, retinal vein occlusion.

Özet

Amaç: Aterojenik plazma indeksi kardiyovasküler hastalık riskini tahmin etmek için kullanılan yeni bir indekstir. Amacımız retinal ven tıkanıklığı ile aterojenik plazma indeksi arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Retinal ven tıkanıklığı olan 24 hasta ve bu hastalarla yaş-cinsiyet ile uyumlu 24 sağlıklı birey retrospektif olarak incelendi. Hasta ve kontrol grubunun demografik özellikleri ve laboratuvar bulguları hastane veri tabanından elde edildi. Aterojenik plazma indeksi trigliseritin molar konsantrasyonunun yüksek yoğunluklu lipoprotein kolesterolüne logaritmik oranı olarak hesaplandı. Aterojenik plazma indeksi, lipid metabolizma parametreleri ve retinal ven tıkanıklığı arasındaki ilişki analiz edildi.

Bulgular: Hasta grubunun yaş ortancası 69,5 (48-86), kontrol grubunun 71,5 (50-84) idi ($p=812$). İki grup arasında total kolesterol ve düşük yoğunluklu lipoprotein kolesterol açısından anlamlı fark olmamasına rağmen ($p=0.458, 0.88$), aterojenik plazma indeksi, hasta grubunda anlamlı olarak yüksekti ($p<0.05$).

Sonuç: Yüksek aterojenik plazma indeksi, klinisyenlere olası retinal ven tıkanıklığı ve retinal ven tıkanıklığına bağlı komplikasyonların önlenmesi için yol gösterici olabilir.

Anahtar Sözcükler: Aterojenik plazma indeksi, lipit parametre, retinal ven tıkanıklığı.

Introduction

Retinal vein occlusion (RVO) is caused by the occlusion of retinal venous vasculature resulting in potential vision loss and long-term sequelae. RVO can be classified as branch RVO (BRVO) and central RVO (CRVO) according to the site of occlusion. CRVO typically occurs at or near the lamina cribrosa of the optic nerve, whereas BRVO occurs at an arteriovenous intersection. The prevalence of BRVO is estimated to be around 0.4% with equal distribution between men and women. The risk of having a RVO episode increases with older age and systemic diseases (1,2). Although the pathogenic mechanisms of RVO are not yet fully understood, a combination of complex elements is believed to contribute to the development of RVO, including compression of the retinal vein at an arteriovenous crossing, increased arterial rigidity and arteriosclerosis, thrombus formation, dysregulated hematologic factors, and elevated levels of proinflammatory mediators and decreased levels of anti-inflammatory cytokines in the vitreous fluid of patients. Previous studies have reported the risk factors for RVO as old age, hypertension, diabetes mellitus (DM), myocardial infarction, cerebral vascular accidents, and chronic kidney disease (CKD) (3-5). A meta-analysis suggested that factors known to contribute to the risk for atherosclerosis might also be important for pathogenesis of RVO (6). However, the precise role of dyslipidemia in the pathogenesis of RVO has not yet been fully identified, and only very limited data on low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and total cholesterol levels in patients with RVO is available (7-9).

Atherogenic index of plasma (AIP), is a novel marker of cardiovascular disease and dyslipidemia (10). AIP is calculated as the logarithmically transformed ratio of molar concentrations of triglycerides (TG) to HDL-C. AIP is accepted as a strong predictor of cardiovascular mortality and it has been shown to increase significantly in coronary artery disease (CAD) and acute coronary syndrome (11,12). Due to the similar etiopathogenesis of CAD and RVO, we hypothesized a possible relation between elevated AIP levels and RVO incidence. To our knowledge, there are no published studies evaluating this relationship.

Material and Method

Twenty-four patients who had the diagnosis of RVO in our department between August 2018 and August 2022 were included in this study. Age and gender matched 24 subjects without retinal vascular pathologies were enrolled for the control group. Exclusion criteria were the presence of liver, kidney and malignant diseases, thyroid dysfunction, and hypolipidemic medication use within the last 2 months. Hospital medical records and patient charts were reached to detect the demographic properties, chronic illness types and laboratory test results of the RVO patients and control subjects. Presence of DM, HT, and CAD was noted. AIP was calculated as the logarithmical ratio of molar concentrations of triglycerides (TG) to HDL-C as [log (TG/HDL-C)].
The study was approved by the Ethics Committee of Ankara Oncology Training and Research Hospital (2022-01/36). All tenets of the declaration of Helsinki have been followed.

Statistical Analysis

Statistical analysis was performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to analyze the normal distribution of the data and Mann-Whitney U test was used to compare two groups. Due to the non-normal distribution of parameters revealed in the test results, the median value, along with the interquartile range, was utilized. To determine the cut-off value and to quantify the parameter accuracy, a receiver operating characteristic curve (ROC) analysis was performed. A statistical significance was considered with a P-value less than 0.05.

Results

Both the RVO and control groups consisted of 24 subjects (14 female, 10 male). All 24 patients included in the study had BRVO. Median age was 69.5 (range, 48-86) in the RVO group and 71.5 (range, 50-84) in the control group ($p=812$). The median value for the LogMAR visual acuity was 1 (0.775-1.3) in the RVO group and 0 (0-0.1) in the control group ($p<0.001$). Of the 24 patients in the RVO group; 22 (91.6%) had HT, 8 (33.3%) had DM, and 7 (29.1%) had CAD. The median value for AIP was 0.586 (0.502-0.614) in the RVO group and 0.295 (0.149-0.433) in the control group ($p<0.001$). Median triglyceride values were also significantly higher in the RVO group compared to the control group (169 (156.25-205) vs. 106 (85-124)), ($p<0.001$). Median HDL-c values were significantly lower in the RVO group compared to the control group (46.45 (41.23-54.25) vs. 53.00 (45.25-64.25)), ($p=0.031$). There were no significant differences between the RVO and the control group median total cholesterol and LDL-c values ($p>0.05$). Biochemical characteristics of the subjects in the RVO group and the control group are summarized in Table I.The ROC analysis revealed a cut off value of 0.425 for AIP to predict RVO incidence with a sensitivity of 95.8% and a specificity of 75% (Figure I).

Table I. Biochemical characteristics of the subjects in the RVO group and the control group

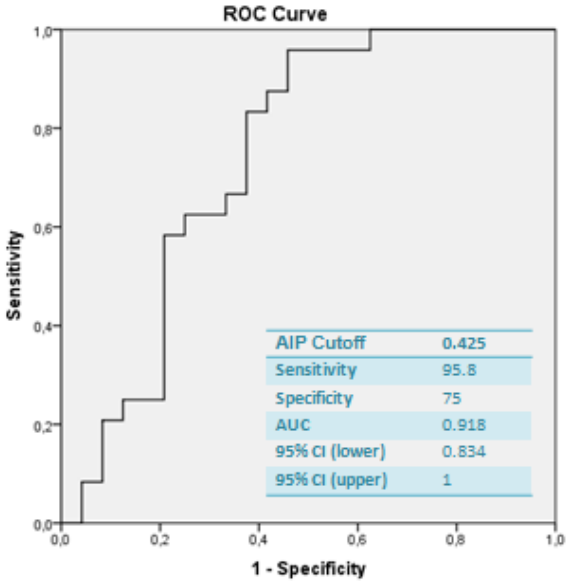
	RVO (n=24)	Controls (n=24)	*p*
Triglycerides (median (interquartile range))	169 (156.25-205)	106 (85-124)	**<0.001**
Total cholesterol (median (interquartile range))	199 (174.27-224.25)	188 (160.75-238.25)	0.458
LDL-c (median (interquartile range))	129 (96.5-166,5)	115.5 (104.5-158)	0.88
HDL-c (median (interquartile range))	46.45 (41.23-54.25)	53.00 (45.25-64.25)	0.031
AIP (median (interquartile range))	0.586 (0.502-0.614)	0.295 (0.149-0.433)	**<0.001**

RVO: Retinal vein occlusion, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, AIP: Atherogenic index of plasma, SD: Standart deviation, **p<0.05*

Discussion

RVO is the second most common retinal vascular disorder following diabetic retinopathy, and it is a major cause of visual impairment (13). RVO is commonly associated with increased cardiovascular morbidity and mortality. Moreover, cardiovascular risk factors such as hypertension, hypercholesterolemia and atherosclerosis have been also implicated in the pathogenesis of RVO (14-16). Epidemiologically, hypertension is the strongest risk factor for RVO. In our study, 91.6% of the RVO patients were detected to have systemic hypertension. Atherosclerosis and dyslipidemia are the two other major risk factors for the development of RVO (2,3). AIP, suggested by Dobiasova and Frohlich in 2000, is a simple atherogenic index calculated as the logarithm of the molar ratio of circulating triglycerides to HDL-C concentrations. Additionally, AIP is inversely related to LDL particle size. In this regard, it has been demonstrated that small dense LDL-C are very vulnerable to oxidative damage and consequently to induce atherosclerotic lesions (17). Furthermore, several scientific studies have used AIP as a prognostic CVD biomarker. AIP is suggested as a potential biomarker (cheap, quick, specific) for the early diagnosis of CVD events (18,19). In our study, considering the role of dyslipidemia as a risk factor for both CVD and RVO, we speculated that AIP could potentially be a biomarker for RVO. As AIP levels were found to be increased in dyslipidemia, we aimed to investigate the predictive role of AIP in RVO incidence, and we found highly elevated AIP levels in RVO patients compared to control subjects. Numerous studies have previously reported that RVO is associated with atherosclerosis which is a chronic inflammatory disease of the arteries (2). Hyperlipidemia is a major risk factor for atherosclerosis and LDL-c is the most abundant atherogenic lipoprotein in the plasma (20). LDL-c leads to the initiation and progression of the atherosclerotic plaque formation in a dose-dependent manner. Therefore, LDL-c is believed to play an important role in the development of RVO (7,8). LDL-c and total cholesterol levels were found to be elevated in the RVO group in our study; however, statistical significance was not reached. In contrast to LDL-c, HDL-c is believed to employ atheroprotective effects. Evidence from various previous reports indicates an association between decreased levels of HDL-c and increased risk of RVO (21). Reverse cholesterol transport mediated by HDL-c deters the accumulation of cholesterol in the arterial wall; hence, prevents the progression of atherosclerosis. HDL-c also inhibits the endothelial inflammatory response and oxidation of LDL-c (22). In our study, we found that RVO patients had significantly lower HDL-c levels

Figure I. The ROC curve analysis for the diagnostic values of Atherogenic index of plasmato differentiate the Retinal Vein Occlusion group from the control group. when compared with the control group.



In recent years, there has been a consensus that non-conventional serum lipid ratios compared to single conventional lipid parameters are better in discriminating the atherogenic events (7-10). It has been also shown that AIP is more effective in predicting cardiovascular disorders and dyslipidemia than the single lipid parameters (11,12). As atherosclerosis is a common risk factor for both CAD and RVO, we aimed to evaluate the predictive value of AIP for RVO

(23). Although AIP was not previously evaluated in RVO patients, there is a study where AIP was found to be highly associated with the severity of visual loss and the second eye involvement in patients with non-arteritic ischemic optic neuropathy (NAİON) (24). It is known that atherosclerosis, DM, HT, and hyperlipidemia also play a major role in the etiopathogenesis of NAİON (24). In parallel, studies involving individuals with type 2 diabetes have revealed a noteworthy connection between the development and severity of diabetic retinopathy and the AIP level (25,26). We found that RVO patients had significantly higher AIP levels than the control group. We also found that AIP levels greater than 0.425 were highly associated with RVO, with a sensitivity of 95.8% and specificity of 75%. Although our study is the first to report a cut off value of AIP for RVO, literature search yields various AIP cut off values reported for systemic diseases. Thus, a cut-off value of 0.54 for AIP in predicting metabolic-associated fatty liver disease in patients with type 2 DM has been reported (sensitivity = 57.8%, specificity = 54.4%) (27). In another study, a cut off value of 0.318 was detected to predict the prognosis of percutaneous coronary intervention, higher AIP indicating unfavorable prognosis (28).

Regarding the pathogenesis of RVO, no treatment has been proved to reverse the obstruction in the vascular system (1,2). The prognosis of RVO is highly variable depending on the location of the vascular occlusion, degree of ischemia, and development of sequelae. Intravitreal injections of the anti-vascular endothelial growth factor (anti-VEGF) agents remains the mainstay of RVO management. Anti-VEGF treatment has been shown to improve vision and to reduce vision-limiting macular edema. However, it is known that 50% of CRVO patients and 30% of RVO patients do not respond to anti-VEGF treatment for macular edema (29). Therefore, as well as the early treatment of RVO, prevention is of the utmost importance. Detection of the accompanying systemic factors might help to prevent the occurrence and subsequent recurrent attacks of RVO. In this study, we aimed to evaluate the predictive role of lipid parameters and AIP for the occurrence of RVO and found a possible relation. We believe that elevated AIP values which is a marker of dyslipidemia might aid clinicians raise suspicion against a possible RVO attack and take precautions accordingly to prevent complications related to RVO.

Retrospective design and small study population are the major limitations of our study. Another limitation of our study is the absence of patients with CRVO in our dataset. Although a multicenter study with larger scale might provide a better insight of the predictive value of AIP in RVO occurrence; our study still provides data of a possible relation between elevated AIP levels and RVO incidence.

Conclusion

To the best of our knowledge, this study is the first to show that AIP, a novel biomarker of dyslipidemia and a strong predictor of cardiovascular mortality, is also associated with the development of RVO. Our study suggests that AIP can aid clinicians to prevent development of RVO and related complications in patient groups under risk.

References

1. Cugati S, Varma DD, Chen CS, Lee AW. Treatment Options for Central Retinal Artery Occlusion. Curr. Treat. Options Neurol 2012;15:63–77.
2. Terao R, Fujino R, Ahmed T. Risk Factors and Treatment Strategy for Retinal Vascular Occlusive Diseases. J Clin Med 2022;11: 6340.
3. Klein R, Klein EB, Moss ES, Meuer SM. The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study. Trans Am Ophthalmol Soc 2000;98:133–143.
4. Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: A systematic review and meta-analysis of prevalence, incidence, and risk factors. J Glob Health 2019;9:010427.
5. Di Capua M, Coppola A, Albisinni R, et al. Cardiovascular risk factors and outcome in patients with retinal vein occlusion. J Thromb Thrombolysis 2009;30:16–22.
6. Janssen MCH, Den Heijer M, Cruysberg JRM, Wollersheim H, Bredie SJH. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. Thrombosis and Haemostasis 2005;93:1021-1026.
7. Zheng C, Lin Y, Jiang B, et al. Plasma lipid levels and risk of retinal vascular occlusion: A genetic study using Mendelian randomization. Front Endocrinol (Lausanne) 2022;13:954453.
8. Stojakovic T, Scharnagl H, März W, Winkelmann BR, Boehm BO, Schmut O. Low density lipoprotein triglycerides and lipoprotein(a) are risk factors for retinal vascular occlusion. Clin Chim Acta 2007;382:77–81.
9. Kim J, Lim DH, Han K, et al. Retinal vein occlusion is associated with low blood high-density lipoproteincholesterol: a nationwide cohort study. American Journal of Ophthalmology 2019;205:35-42.
10. Szapary PO, Rader DJ. The triglyceride-high-density lipoprotein axis: an important target of therapy? Am Heart J 2004;148:211-221.
11. Fernández-Macías JC, Ochoa-Martínez AC, Varela-

Silva JA, Pérez-Maldonado IN. Atherogenic Index of Plasma: Novel Predictive Biomarker for Cardiovascular Illnesses. Arch Med Res 2019;50:285-294.
12. Onen S, Taymur I. Evidence for the atherogenic index of plasma as a potential biomarker for cardiovascular disease in schizophrenia. J Psychopharmaco 2021;l35:1120-1126.
13. Buehl W, Sacu S, Schmidt-Erfurth U. Retinal vein occlusions. Dev Ophthalmol 2010;46:54-72.
14. Terao R, Fujino R, Ahmed T. Risk Factors and Treatment Strategy for Retinal Vascular Occlusive Diseases. J Clin Med 2022;11: 6340.
15. Klein R, Klein EB, Moss ES, Meuer SM. The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study. Trans Am Ophthalmol Soc 2000;98:133–143.
16. Wong TY, Larsen EK, Klein R, et al. Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities & Cardiovascular Health studies. Ophthalmology 2005;112:540–547.
17. Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem 2001;34:583-588.
18. Fernández-Macías JC, Ochoa-Martínez AC, Varela-Silva JA, Pérez-Maldonado IN. Atherogenic Index of Plasma: Novel Predictive Biomarker for Cardiovascular Illnesses. Arch Med Res 2019;50:285-294.
19. Zhang Y, Chen S, Tian X, et al. Association between cumulative atherogenic index of plasma exposure and risk of myocardial infarction in the general population. Cardiovasc Diabetol 2023; 17;22:210.
20. Hurtubise J, McLellan K, Durr K, Onasanya O, Nwabuko D, Ndisang JF. The different facets of dyslipidemia and hypertension in atherosclerosis. Curr Atheroscler Rep 2016;18:82.
21. Von Eckardstein A, Nofer JR, Assmann G. High density lipoproteins and arteriosclerosis role of cholesterol efflux and reverse cholesterol transport. Arterioscler Thromb Vasc Biol 2001;21(1):13–27.
22. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL.Circ Res 2004;95:764–772.
23. Naito HK. The association of serum lipids, lipoproteins, and apolipoproteins with coronary artery disease assessed by coronary arteriography. Ann N Y Acad Sci 1985;454: 230-238.
24. Koçak N, Yeter V, Turunç M, Bayrambaş M, Eraydın B, Güngör İ. Atherogenic indices in non-arteritic ischemic optic neuropathy. Int J Ophthalmo l2021;14:1041-1046.
25. Xu J, Zhou H, Xiang G. Association of Atherogenic Index of Plasma With Retinopathy and Nephropathy in Adult Patients With Type 2 Diabetes Mellitus Aged > 18 Years. Can J Diabetes 2022; 29:S1499-2671(22)00092-2.
26. Namitha D, Nusrath A, Asha Rani N, et al. Role of Lipid Indices in the Assessment of Microvascular Risk in Type 2 Diabetic Retinopathy Patients. Cureus 2022;22;14:e23395.
27. Samimi S, Rajabzadeh S, Rabizadeh S, et al. Atherogenic index of plasma is an independent predictor of metabolic-associated fatty liver disease in patients with type 2 diabetes. Eur J Med Res 2022;27:112.
28. Qin Z, Zhou K, Li Y, et al. The atherogenic index of plasma plays an important role in predicting the prognosis of type 2 diabetic subjects undergoing percutaneous coronary intervention: results from an observational cohort study in China. Cardiovasc Diabetol 2020;19(1):23.
29. Chatziralli I, Theodossiadis G, Chatzirallis A, Parikakis E, Mitropoulos P, Theodossiadis P. Ranibizumab for retinal vein occlusion: Predictive Factors and Long-Term Outcomes in Real-Life Data. Retina 2018;38(3):559-568.

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Management of Cutaneous Mastocytosis during Childhood: Update from the Literature

Çocukluk Döneminde Kutanöz Mastositoz Yönetimi: Literatürden Güncelleme

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Management of Cutaneous Mastocytosis during Childhood: Update from the Literature

Abstract

Cutaneous mastocytosis defines a group of diseases categorized by the existence of augmented numbers of mast cells in the dermis. Cases with cutaneous mastocytosis do not meet diagnostic conditions for systemic mastocytosis and demonstrate no proof of organ participation other than the dermis. This article after mentioning history, prevalence, and classification briefly reviews clinical features and triggers of mast cell activation and lastly discusses the management of cutaneous mastocytosis under the light of current observations in detail. Patients with cutaneous mastocytosis often be influenced by mast cell mediator-linked symptoms, which are often commenced by pressures on the dermal lesions. Management of cutaneous mastocytosis is chiefly built on avoiding triggers of mast cells. The availability of epinephrine autoinjectors in case of severe systemic reactions such as anaphylaxis and utilizing antihistamines when symptoms occur to establish the backbone of treatment in cutaneous mastocytosis cases.

Keywords: Children, cutaneous mastocytosis, mast cell, mastocytoma, pediatric mastocytosis, urticaria pigmentosa.

Özet

Kutanöz mastositoz, dermiste artan sayıda mast hücrelerinin varlığına göre kategorize edilen bir hastalık grubunu tanımlar. Kutanöz mastositozlu vakalar, sistemik mastositoz için tanısal koşulları karşılamaz ve dermis dışında herhangi bir organ katılımı kanıtı göstermez. Bu yazıda tarih, prevalans ve sınıflandırmadan bahsedildikten sonra mast hücre aktivasyonunun klinik özellikleri ve tetikleyicileri kısaca gözden geçirilmekte ve son olarak kutanöz mastositozun yönetimi güncel gözlemler ışığında detaylı olarak tartışılmaktadır. Kutanöz mastositozlu hastalar sıklıkla, dermal lezyonlar üzerindeki baskı/basınç ile tetiklenen mast hücre mediatörüne bağlı semptomlardan etkilenir. Kutanöz mastositozun yönetimi esas olarak mast hücre tetikleyicilerinden kaçınma üzerine kuruludur. Anafilaksi gibi şiddetli sistemik reaksiyonlar durumunda epinefrin otoenjektörlerinin mevcudiyeti ve semptomlar ortaya çıktığında antihistaminiklerin kullanılması kutanöz mastositoz vakalarında tedavinin temel unsurunu oluşturur.

Anahtar Sözcükler: Çocuklar, kutanöz mastositoz, mast hücresi, mastositoma, pediatrik mastositoz, ürtiker pigmentosa.

Introduction

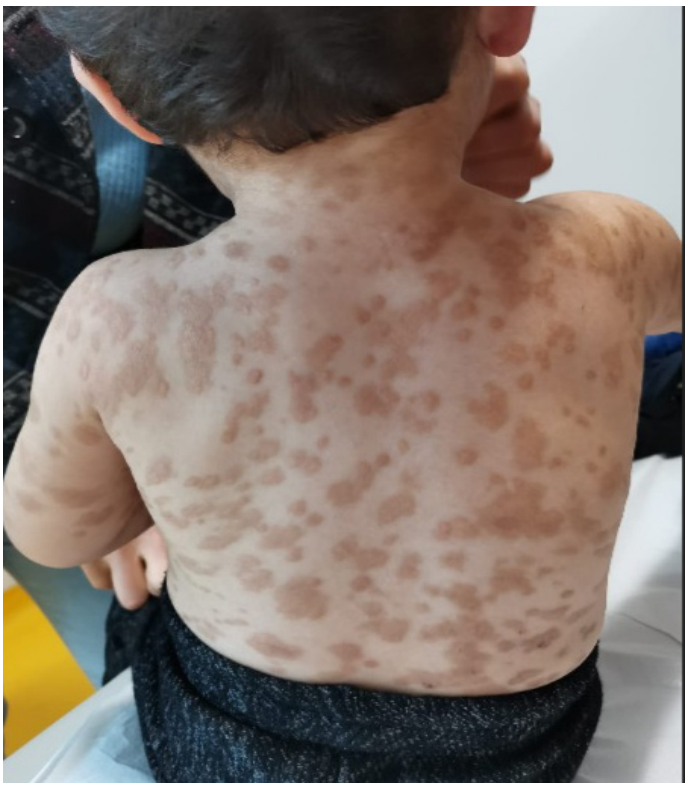
Cutaneous mastocytosis (CM) defines a group of diseases categorized by the existence of increased numbers of mast cells (MCs) in the dermis. Cases with CM do not meet diagnostic conditions for systemic mastocytosis and demonstrate no proof of organ participation other than the dermis (1).

This article after mentioning the history, prevalence, and classification of CM will review different clinical features and triggers of MC activation and lastly discusses the management of CM in children under the light of current literature in detail.

History, Prevalence, and Classification

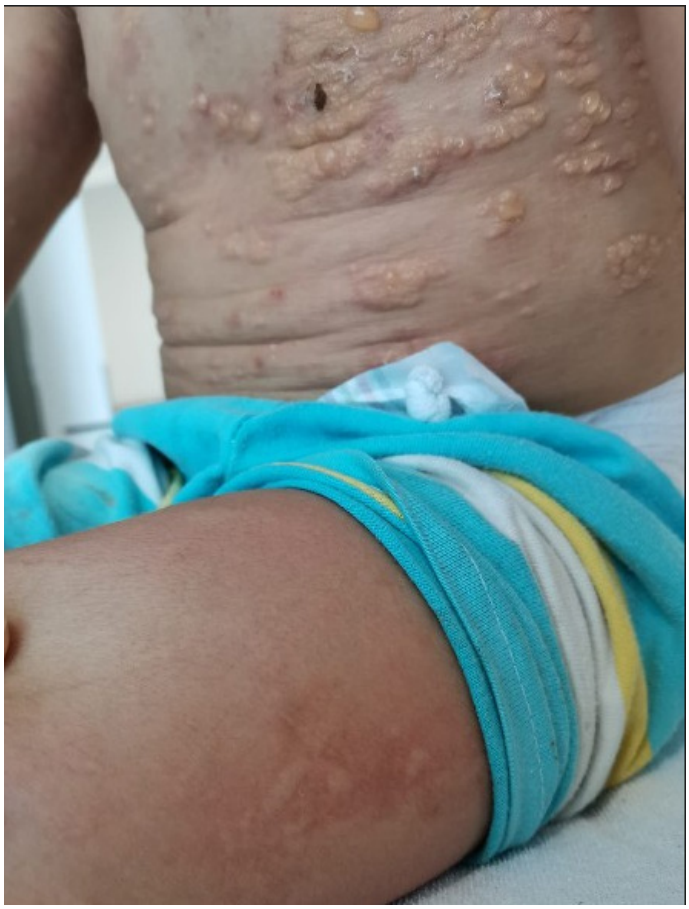
In 1878, Sangester first time called this disease urticaria pigmentosa (UP) to define dermal lesions (2), while the term 'CM' was first introduced in 1936 by Sezary and Chauvillon (3). Cutaneous mastocytosis is a relatively frequent condition in pediatric dermatology clinics. Sagher and Even-Paz found that its prevalence ranged from 1: 1.000 to 1: 8.000 dermatology patients in the USA (4), whereas Torrelo et al. report 5.4 cases per 1.000 pediatric dermatology cases in Spain (5) and it was noted to be 1: 500 first-time pediatric dermatology cases (6).

Figure I. Maculo-papular cutaneous mastocytosis in one of our patients



The WHO divides CM into three main categories: Maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM), and solitary skin mastocytoma (Figure 1 and 2). If CM contains ≤3 lesions are named mastocytomas whereas MPCM is between 4 and 100 dermal lesions. The DCM category involves diffuse cutaneous involvement (7-10).

Figure II. Diffuse cutaneous mastocytosis appearance in one of our patients



Review of different clinical features in case series of CM in literature

Incidence of various clinical presentations in childhood CM reported being different in the literature. The largest assessment of CM included 1,747 cases over 54 years. While the most common symptom was pruritus seen in 48% of the cases, blistering was described in a third of the pediatric patients, flushing in 25%, digestive symptoms in 20%, and anaphylaxis in 5% (9,11). Isolated pulmonary symptoms e.g., rhinorrhea or bronchospasm due to MC mediators are infrequently seen in CM (9,12,13). Another retrospective series had 71 cases of CM, 53 with UP, 12 mastocytomas, and 6 DCM; 94% of the cases manifested with positive Darier's sign, 92% had an onset in the first year of childhood, and 80% better or had natural resolution of disease in time (6). The most common skin lesion was macules, subsequently plaques or papules, and bullae in 16 cases. Accompanying symptoms and signs were lacking in mastocytoma cases excluding itching; diarrhea was present in 7 out of 36 UP cases and

2 of 5 DCM (12).

Among 65% of UP cases, 20% presented at birth and 80% during the first year of life in a retrospective review of 180 patients with CM. Of the 117 cases of UP, 13 were familial and only one generation was affected in 5 affected families. No familial history was reported in mastocytoma cases. Of the mastocytoma cases, 75% and 56% of UP cases had full resolution of the lesions over a 1-15-year follow-up period. Associated symptoms in UP cases involved asthma in 10.3%, flushing in 12.8%, fever in 1.7%, and abdominal pain in 2% (14).

Triggers of Mast Cell Activation

Triggers MC activation include certain foods, cold water, hot baths, exercise, heat, venoms, rubbing of cutaneous lesions, alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), polymyxin B, narcotics, anticholinergics and some general anesthetic drugs (table 1). When exposed to certain triggers, MC release mediators such as histamine, eicosanoids, prostaglandins, leukotrienes, heparin, proteases, and certain cytokines causing the symptoms of mastocytosis (7,15). Different histamine-containing nutrients, including treated meats, smoked fish, ripened cheeses, fermented foods, eggplant, and spinach, and histamine-releasing nutrients such as citrus fruits, strawberries, pineapple, tomatoes, nuts, shellfish, chocolate, and additives are thought to be triggers (8).

Treatment Prophylactic treatment

General measures include avoidance of any triggers, such as sudden temperature changes, and rubbing of lesions (table 1). The triggering factors need to be taught to patients and parents, such as heat, cold, sudden changes in temperature, moisture, stroking of skin lesions, sleep deprivation, exercise, emotional stress, spicy food, and febrile illnesses (14,15). Additionally, parents should recognize the drugs that can result in MC activation including morphine, codeine, vancomycin, aspirin, ketorolac, and muscle relaxant drugs (16).

Surgical treatment

In certain patients, if Darier's sign can be generated simply and physical exposure is unavoidable daily encounters, concealing the cutaneous lesion with an adhesive bandage or shielding dress can be of help (15). Surgical removal only ought to be debated in very unusual conditions, e.g. irritable solitary mastocytomas in a critical site or for the risk of induction of anaphylaxis in profoundly penetrated mastocytoma (16).

Table I. Triggers of mast cell activation

Environmental	
Sudden temperature changes	Heat, cold, moisture
Pressure	
Friction/rubbing/ stroking	
Sunlight	
Allergens	Venom, pollen, molds, mite, food, etc.
Human Body	
Exercise	
Teething	
Fever	
Infections	
Endoscopy (GIS operation)	
Sleep deprivation	
Emotions	Stress, Anxiety
Drugs	
Analgesics (NSAIDs)	Aspirin, ketorolac
Opioid/narcotics	Morphine, codeine
Systemic anesthetics	
Muscle relaxants	Atracurium, mivacurium, vecuronium, pancuronium, cisatracurium
Polymyxin B	
Anticholinergics	
Radiocontrast media	
Antibiotics	Vancomycin
Vaccinations	
Cough suppressants	
IFN- α 2b	
Dietary	
Alcohol	
Caffeine	Chocolate
Spices	
Fermented food	Aged cheeses
Cured meats	
Smoked fish	
Bacterial toxins	
Additives	
Food containing histamine	Eggplant, spinach
Histamine-releasing foods	Citrus fruits, nuts, shellfish, strawberries, pineapple, tomatoes

Management during operation

The risk of perioperative anaphylaxis in children with CM even with widespread dermal participation and high serum tryptase levels is low. The most pronounced nonspecific histamine-releasing drugs, opiates and neuromuscular blocking agents/muscle relaxants such as atracurium and mivacurium should be avoided if possible or administered slowly. On the other hand vecuronium, pancuronium, cisatracurium and fentanyl and related agents have not been reported to cause significant perioperative reactions. In the perioperative period, it is essential to have adrenaline

and isoflurane available (7). Postoperatively, with care, we can select paracetamol (17). Intradermal skin testing of drugs utilized in general anesthesia and muscle-relaxing agents should be considered preoperatively. Patterson protocol could be used for procedures involving intravenous contrast due to the increased risk of anaphylaxis and other reactions due to anesthesia (7). The risk can be diminished using a supplementary intravenous premedication of H1-/H2-antihistamines 1-2 hr (or clemastine 0.05 mg/kg orally divided q8-12hr) and prednisone 12-24 h/1-2 hr prior operation (bolus 2 mg/kg and then 1 mg/kg; respectively), and/or sedatives as required on the operation day (7,9). Before the surgical intervention, decreasing anxiety or even preoperative sedation (oral diazepam) can be recommended (table 2).

Table II. Therapeutic options for cutaneous mastocytosis

Therapeutic options	
Prophylactic treatment	The triggering factors need to be taught to patients and parents
Surgical treatment	Concealing the cutaneous lesion, surgical removal
Management during operation	Keep adrenaline and isoflurane available, use paracetamol instead of NSAIDs, Intradermal skin testing of drugs and Patterson protocol if necessary
General management in CM	Oral H1 and/or H2 antihistamines, anti-leukotriene (montelukast), oral disodium cromoglycate, PUVA
Topical treatment	Topical corticosteroid, pimecrolimus, tacrolimus, disodium cromoglycate (1- 4%)
Self-injectable epinephrine	Adrenaline autoinjector
Biologicals	Omalizumab and Nemolizumab

PUVA: methoxy psoralen treatment with long-wave ultraviolet A radiation; CM: cutaneous mastocytosis; NSAID: nonsteroidal anti-inflammatory drugs.

General management in CM

Oral H1 and/or H2 antihistamines help control the itching and flushing in UP. Prophylactic oral non-sedating antihistamines, e.g. cetirizine, in children who have not yet demonstrated any symptoms can be recommended. In patients with persistent symptoms, H2 antihistamine or anti-leukotriene (montelukast) can be added to the treatment schedule (9). H2 antihistamines (cimetidine, famotidine), or proton pump inhibitors, (e.g., omeprazole, pantoprazole, lansoprazole) may provide help with gastrointestinal system (GIS) symptoms including abdominal pain, cramping, and diarrhea. Oral disodium cromoglycate is also can be used for digestive symptoms (15-20 mg/kg/d divided into 3 doses) (9).

Severe CM types, e.g. diffuse bullous disease, or life-threatening MC-mediator release types can profit from oral methoxy psoralen treatment with long-wave ultraviolet A radiation (PUVA). Although phototherapy with ultraviolet A (UVA)1 light, narrowband UVB, or PUVA treatment can heal the cutaneous lesion, it should only be utilized in certain patients with possible carcinogenic risk in mind in generally self-healing pediatric CM. PUVA is most helpful in non-hyperpigmented diffuse bullous disease while the response is typically weak in nodular or plaque types (9,12).

Topical treatment

In solitary mastocytomas, the local utilization of a strong topical glucocorticosteroid can be useful by reducing itching and improving cosmetic issues in cases with recurrent pruritus. Mild or medium potent glucocorticosteroids are better in infants; mometasone furoate 0.1% cream can be considered in a newborn with DCM. High potent glucocorticosteroids such as clobetasol propionate 0.05% may be used for solitary mastocytoma therapy (16). Systemic corticosteroid efficiency has been seen in a few cases of severe skin disease. However, adverse effects on the dermis such as atrophy and adrenocortical suppression are limiting factors in their long-term use (table 2).

Topical pimecrolimus with excellent results and its safety profile is recommended instead of corticosteroids in pediatric CM. Calcineurin inhibitors, pimecrolimus, and tacrolimus were shown to decline the density of murine dermal MCs and histamine synthesis by tempting MC apoptosis. Furthermore, pimecrolimus has a noteworthy anti-inflammatory effect by preventing T-cell stimulation, hindering inflammatory cytokine production, and immunomodulatory effects with a weak systemic immunosuppressive potency (15,16). Topical treatment with 1% pimecrolimus cream utilized twice daily on MPCM and mastocytoma lesions in 18 children with CM with a mean duration of 8.3 months, some of the lesions have regressed, and even a few vanished. Clinical assessment 12 months after the completion of treatment, no recurrence of the cutaneous lesions that had resolved was observed (18). Disodium cromoglycate at 1% to 4% concentration in an aqueous solution or mixed with a water-based emollient cream may also diminish itching.

Self-injectable epinephrine (adrenaline autoinjector)

Self-injectable epinephrine in CM is suggested in children with DCM, blistering, or signs of systemic mastocytosis (SM), prior anaphylaxis attacks, and/or high baseline serum tryptase concentration (15,19).

Biologicals (Omalizumab and Nemolizumab)

A recombinant humanized monoclonal antibody that prevents the attaching of IgE to the FcεRI receptor on the surface of MCs, displayed a swift and long-term

efficiency to regulate severe MC-linked symptoms in an adolescent with recurrent anaphylaxis attacks. Studies have demonstrated that utilizing anti-IgE (omalizumab) decreases exacerbations in pediatric CM cases (15).

Since pruritus is stimulated by increased IL-31 levels and nemolizumab, a specific IL-31 antibody that is presently under development, its therapeutic utilization in severe types of CM would provide potential benefit if this drug becomes obtainable in the future (8).

Prognosis in various studies of the literature

If CM persists beyond adolescence, up to 10% of cases may advance into systemic form with a guarded prognosis (7). Among the 66 cases with CM, one developed into an indolent SM with bone marrow participation. She had skin findings of itching, wheals, and blistering from 6 months of age subsequently progressive, persistent systemic symptoms of wheezing, dizziness, and angioedema and she was diagnosed with indolent systemic mastocytosis at the age of 19 (20).

In one retrospective study where medical archives and follow-up examinations were accessible for 25 children with MPCM, with monitoring of 5 years, 76% resolved, 16% had stable disease, one had complete improvement, and one deteriorated (6). In another prospective study, 55 cases with MPCM were followed for at least 2 years, during which 9% of all cutaneous lesions had been involuted (13). In 1963, a study by Caplan et al concluded from analysis and follow-up of 112 cases that the outcome of CM patients was fatal in 2.9% (21). In a review of 67 pediatric cases, the average follow-up was 4.1 years, 36% had demonstrated resolution over 6.1 years, and 55% of the cases stayed unchanged (22). In the fifth retrospective study with a follow-up of 1- to 15 years, 35 of 62 cases with MPCM (56%) demonstrated complete regression (14). In the sixth study, 10 of 15 patients had complete improvement of the dermal disorder and symptoms at follow-up approximately of 20 years (23). In a current review of the literature, it could progress into a systemic form in around 1/100 cases with CM (15).

Conclusion

CM is confined to the skin and it occurs almost exclusively in children. CM is divided into three main categories: MPCM, DCM, and mastocytoma. Several dermatological and/or systemic pathologies should be ruled out in the differential diagnosis. All CM cases should be assessed for systemic disease development, especially in the existence of other risk factors. The prognosis of CM is superb, particularly if the CM's inception is in the first two years of life.

References

1. Golkar L, Bernhard DJ. Mastocytosis. Lancet1997; 349: 1379 –1385.
2. Sangster A. An anomalous mottled rash, accompanied by pruritus, factitious urticaria and pigmentation, 'urticaria pigmentosa (?)' Trans. Clin. Soc. Lond. 1878; 11:161–163.
3. Sezary ALCG, Chauvillon P. Dermographisme et mastocytose. Bull. Soc. Fr. Dermatol. Syph. 1936; 43:359–361.
4. Sagher FR, Even-Paz Z. Mastocytosis and the Mast Cell. Year Book Medical Publishers, Chicago, 1967.
5. Torrelo FA, Navarro CL, Escribano ML, Zambrano AZ. Estudios clínicos y de laboratorio: diagnóstico, tratamiento y clasificación de la mastocitosis pediátrica. Estudio de 172 casos. Actas Dermosif 1998; 89:461-476.
6. Kiszewski AE, Durán-Mckinster C, Orozco-Covarrubias L, Gutiérrez-Castrellón P, Ruiz-Maldonado R. Cutaneous mastocytosis in children: a clinical analysis of 71 cases. J Eur Acad Dermatol Venereol. 2004; 18:285-90.
7. Sandru F, Petca RC, Costescu M, et al. Cutaneous mastocytosis in childhood-Update from the Literature. J Clin Med. 2021; 10: 1474.
8. Macri A, Cook C. Urticaria Pigmentosa. 2021 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29494109.
9. Nemat K, Abraham S. Cutaneous mastocytosis in childhood. Allergol Select. 2022; 6:1-10.
10. Horny HP, Metcalfe DD, Bennet JM, et al. Mastocytosis. In: WHO Classification of the Tumors of Haematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele H, Vardiman JW. (Eds), IARC, Lyon 2008. p.54
11. Meni C, Georgin-Lavialle S, Le Saché de Peufeilhoux L, et al. Paediatric mastocytosis: long-term follow-up of 53 patients with whole sequencing of KIT. A prospective study. Br J Dermatol. 2018; 179: 925–932.
12. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: practical recommendations. Am J Clin Dermatol. 2011; 12:259-270.
13. Akoglu G, Erkin G, Cakir B, et al. Cutaneous mastocytosis: demographic aspects and clinical features of 55 patients. J Eur Acad Dermatol Venereol 2006;20:969–973
14. Ben-Amitai D, Metzker A, Cohen HA. Pediatric cutaneous mastocytosis: a review of 180 patients. Isr Med Assoc J 2005;7:320–322.
15. Giona F. Pediatric Mastocytosis: An Update. Mediterr J Hematol Infect Dis. 2021; 13(1): e2021069.
16. Lange M, Hartmann K, Carter MC, et al. Molecular Background, Clinical Features and Management of

Pediatric Mastocytosis: Status 2021. Int J Mol Sci. 2021; 22:2586.
17. Bonadonna P, Lombardo C, Zanotti R. Mastocytosis and allergic diseases. J Investig Allergol Clin Immunol. 2014; 24:288-297
18. Mashiah J, Harel A, Bodemer C, et al. Topical pimecrolimus for pediatric cutaneous mastocytosis. Clin Exp Dermatol. 2018; 43: 559–565.
19. Ertugrul A, Baskaya N, Cetin S, Bostanci I. Anaphylaxis and epinephrine autoinjector use in pediatric patients with cutaneous mastocytosis. Pediatr Dermatol. 2021; 38(5):1080-1085. doi: 10.1111/pde.14800.
20. Sathishkumar D, Balasundaram A, Mathew SM, et al. Clinicopathological profile of childhood onset cutaneous mastocytosis from a tertiary care center in south India. Indian Dermatol Online J. 2021; 12:706-713.
21. Caplan RM. The natural course of urticaria pigmentosa. Analysis and follow-up of 112 cases. Arch Dermatol 1963; 87:146–157.
22. Azana JM, Torrelo A, Mediero IG, et al. Urticaria pigmentosa: a review of 67 pediatric cases. Pediatric Dermatology. 1994; 11:102–106.
23. Uzzaman A, Maric I, Noel P, Kettelhut BV, Metcalfe DD, Carter MC. Pediatric-onset mastocytosis: a long term clinical follow-up and correlation with bone marrow histopathology. Pediatr Blood Cancer 2009; 53:629-634.

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Extrahepatic Intra-abdominal Hydatid Cyst Detected Incidentally After Trauma: A Case Report

Travma Sonrası İnsidental Tespit Edilen Ekstrahepatik İntraabdominal Kist Hidatik: Olgu Sunumu

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Extrahepatic Intra-abdominal Hydatid Cyst Detected Incidentally After Trauma: A Case Report

Abstract

Hydatid cyst is a parasitic disease frequently encountered in the liver and lungs, caused by the larval form of *Echinococcus granulosus*. Occasionally, hydatid cysts can be seen in the spleen, kidney, heart, bone, ovaries, and peritoneal cavity. We presented a case of extrahepatic intra-abdominal hydatid cyst, which we detected incidentally in an eight-year-old girl who was investigated for post-traumatic abdominal pain. A radiologic examination of the patient showed a midline cystic mass including septations superior to the bladder, and mesenteric cyst, ovarian mass, and hydatid cyst were considered for differential diagnosis. The indirect hemagglutination (IHA) test result of the patient was negative (<1/160), and the diagnosis of hydatid cyst was made by the histopathological evaluation and microscopic examination of cyst fluid following the removal of cystic mass which was well circumscribed by omentum. We believe that extrahepatic hydatid cysts should be considered in the differential diagnosis of intra-abdominal cystic masses, particularly in endemic regions.

Keywords: Cystic mass, extrahepatic, hydatid cyst, trauma.

Özet

Kist hidatik, *Echinococcus granulosus*'un larval formunun neden olduğu sıklıkla karaciğer ve akciğerlerde karşılaşılan paraziter bir hastalıktır. Nadiren de olsa dalak, böbrek, kalp, kemik, overler ve peritoneal kavitede kist hidatik görülebilir. Travma sonrası karın ağrısı nedeniyle araştırılan 8 yaşında bir kız hastada insidental olarak tespit ettiğimiz extrahepatik intraabdominal kist hidatik olgusu sunduk. Radyolojik incelemede orta hatta mesane superiorunda septasyon gösteren kistik kitle saptanan hastada mezenter kisti, over kaynaklı kitle ve kist hidatik ayırıcı tanılarda düşünüldü. İndirekt hemaglütinasyon (İHA) testi sonucu negatif (<1/160) olarak raporlanan hastada operasyon sırasında çıkarılan düzgün sınırlı omentumla sarılı kistik kitlenin histopatolojik değerlendirilmesi ve kist sıvısının mikroskobik incelenmesiyle kist hidatik tanısı konuldu. Özellikle endemik bölgelerde karın içi kistik kitle saptanan olgularda ekstrahepatik kist hidatik ayırıcı tanıda düşünülmesi kanaatindeyiz.

Anahtar Sözcükler: Ekstrahepatik, kist hidatik, kistik kitle, travma.

Introduction

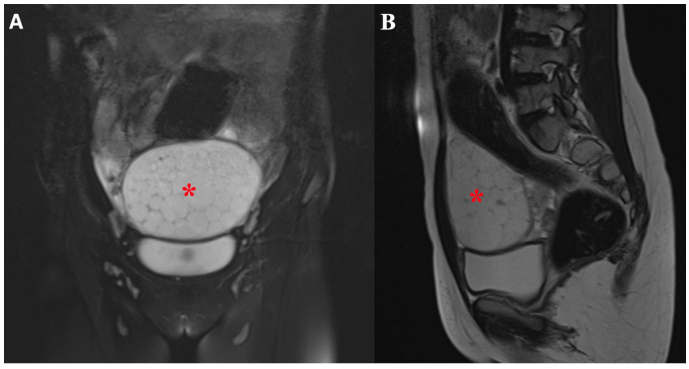
Hydatid cyst is a parasitic disease often encountered in the liver and lungs, caused by the larval form of *Echinococcus granulosus*. Although it is a rare occasion, hydatid cysts can be seen in the spleen, kidney, heart, bone, ovaries, and peritoneal cavity (1,2,3). Uncomplicated hydatid cysts are usually asymptomatic. Although the symptoms are usually due to the complications, symptoms may also occur as a result of compression of extensively growing cysts (4).

We present a case of extrahepatic intra-abdominal hydatid cyst, which we detected incidentally in a patient who was investigated for post-traumatic abdominal pain. An informed consent form was obtained from the patient's parents for this case report.

Case presentation

An 8-year-old girl was admitted to our emergency department with a history of falling from a height. The patient was complaining of abdominal pain, and she did not have any physical examination findings except for lower abdominal quadrant tenderness. Complete blood count and serum biochemical values were within normal limits (Hb: 12.3 g/L, WBC: 9.8x103/µL, ALT: 15.3 IU/L, AST: 30.3 IU/L). The abdominal ultrasonography (US) of the patient showed a 75x50 mm cystic mass adjacent to the superior of the bladder. Intra-abdominal solid organs were considered normal. A conservative in-patient follow-up was planned for the trauma patient, and contrast-enhanced magnetic resonance imaging (MRI) was performed to evaluate the cystic mass in detail. The MRI detected a midline cystic mass 73 x 100 mm in size within the pelvis, with an oval appearance and smooth contours, showing thin diffuse septations after contrast agent injection (Figure 1). There was no additional pathologic finding in the intra-abdominal solid organs. For the cystic mass, the differential diagnosis of mesenteric cyst, ovarian mass, and hydatid cyst were considered. However, the indirect hemagglutination (IHA) test result of the patient was reported as negative (<1/160). The exploratory laparotomy of the patient revealed a well-circumscribed cystic mass surrounded by the omentum adjacent to the bladder in the pelvic region, and peritoneal surface was covered with multiple millimetric-sized cystic structures. The cystic mass was removed along with the surrounding omentum (Figure 2). Additionally, cystic structures on the peritoneal surface were excised for histopathological and microbiological sampling. The direct microbiological examination of the cyst fluid showed protoscolex structures. As well as histopathological examination revealed findings in favor of hydatid cyst. Albendazole treatment was started on the patient who had no postoperative problems, the treatment was continued for 6 months, and no recurrence was observed during the 1-year follow-up.

Figure I. Coronal (A) and sagittal (B) view of the cystic mass with septations adjacent to the superior of bladder demonstrated with asterisk on MRI images.



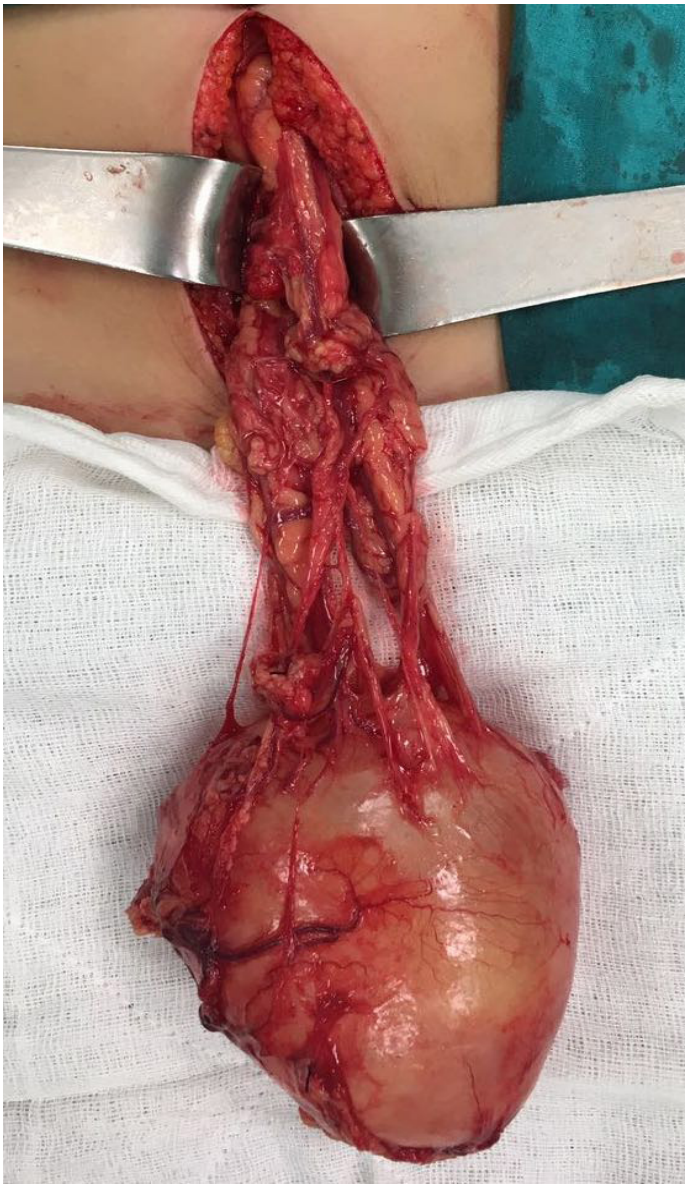
Discussion

Particularly in endemic regions hydatid cysts should be considered in the differential diagnosis of intra-abdominal cystic lesions in children. Although hydatid cysts are usually encountered in the liver and lungs, they can be seen anywhere in the body. However, primary omental hydatid cyst is an extremely rare condition. Symptoms of hydatid cyst disease usually depend on the location and size of the cyst. Abdominal distension and pain, nausea, vomiting, and urinary symptoms due to bladder compression may be observed. US, CT, and MRI are the most utilized radiological examinations for the diagnosis of liver hydatid cyst disease, nevertheless, preoperative diagnosis of isolated intra-abdominal disease is quite difficult (5). The sensitivity of IHA, which is one of the serological tests used in the diagnosis of hydatid cysts can decrease to 52.2% depending on various factors (6). It has been reported that the sensitivity of serological tests is lower in cases with extrahepatic localization as compared to liver hydatid cysts (6,7). Similarly, in our case, preoperative radiologic examinations and IHA tests were not helpful for the definitive diagnosis. The diagnosis of a hydatid cyst was made after surgical exploration of the case with the histopathological and microbiological examination of the removed cyst covered with omentum.

As an endemic parasitic disease in our country, Echinococcus alveolaris disease should also be considered in the differential diagnosis of such cystic masses, which may pretend a malignant disease by spreading from liver to various tissues including lungs, spleen, kidney, pancreas, lymphoid tissues,

bone, ovaries, adrenal gland, and cerebrum (8).

Figure II. Operative image of the intra-abdominal hydatid cyst surrounded by omentum.



Surgery is important in both the diagnosis and treatment of intra-abdominal hydatid disease. The ideal treatment is to excise the entire cyst by careful dissection, and separating it from the surrounding organs without rupturing, to prevent spread and contamination (9). For this purpose, operative treatment is performed with open and laparoscopic surgical techniques. Since we did not have a definitive preoperative diagnosis, we preferred open surgery for our patient.

In conclusion, hydatid disease should be considered in the differential diagnosis of intra-abdominal cystic lesions in children, particularly in endemic regions. It should be kept in mind that using imaging methods and laboratory tests alone in the diagnosis may especially miss extrahepatic hydatid disease.

References

1. Kütükçü E, Kapan S, Turhan AN, Ede B, Aygün E. Pankreatik kist hidatik: Olgu sunumu. Bakırköy Tıp Dergisi 2005; 1: 74-76.
2. Balik AA, Çelebi F, Basoglu M, Oren D, Yildirgan, Atamanalp SS. Intra-abdominal extrahepatic echinococcosis. Surg Today 2001; 31: 881-884.
3. Topçu R, Sezikli İ, Erkent M, et al. Ekstrahepatik yerleşimli primer intraabdominal kist hidatiklere cerrahi yaklaşım. Turkish Journal of Clinics and Laboratory 11(5), 419-423.
4. Oneto AR, Salgueiro FO, Fiorentino JA, et al. A complicated liver hydatid: experience at one center. Cir Pediatr 1998; 11:30-36.
5. Erkan N, Yıldırım M, Özdemir DA, Akdeniz S, Boz A, Polat AF. Dev intraabdominal hidatid kist: Preoperatif tanı zorluğu ve tedavisi. Akademik Gastroenteroloji Dergisi 2004; 3: 39-41.
6. El-Sherbini M, Yousif A, Ismail S, Abdelraouf A, Abdel-Shafi I. Anatomical patterns of intrahepatic cystic echinococcosis in reference to serological and clinical findings. Parasitologists United Journal 2020; 13(2): 107-113.
7. Guraya SY, Alzobydi AH, Guraya SS. Primary extrahepatic hydatid cyst of the soft tissue: a case report. J Med Case Rep 2012 Nov 26;6:404
8. Aras Y, Sabancı AS, Boyalı O. ve ark. Kraniyal Metastazlı Alveolar Ekinokok: Olgu Sunumu ve Literatürün Gözden Geçirilmesi. Türk Nöroşir Derg 2014, Cilt: 24, Sayı: 3, 298-305
9. Prousalidis J, Tzardinoglou K, Sgouradis L, Katsohis C, Aletras H. Uncommon sites of hydatid disease. World J Surg 1998; 22: 17-22.

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When Words Matter Most: Conveying Serious Health Information to Parents

Kelimelerin En Önemli Olduğu Zamanlar: Ciddi Sağlık Bilgilerinin Ebeveynlere Aktarılması

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When Words Matter Most: Conveying Serious Health Information to Parents

Dear Editor,

We write in reflection on the profound issues presented by the excellent article authored by Dr. Karakaş (1). The art of medicine extends beyond the confines of diagnosis and treatment; it comprehends the profound responsibility of conveying complex health information to patients and, in the case of minors, their guardians. The original Dr. Karakaş discourse (1) laid a substantial foundation on the general principles of patient communication, emphasizing clarity, empathy, and ethical consideration. However, we would like to offer a complementary perspective on the casuistry of pediatric communication shows unique challenges and requires a tailored approach that is sensitive to the developmental, emotional, and cognitive capacities of both child and parent.

A diagnosis of a serious illness is a life-altering event for anyone, but when the subject of such news is a child, the dynamics of this communication become even more delicate. Parents or guardians bear the dual burden of comprehending the medical reality and supporting their children through the ensuing journey. Healthcare professionals must adopt strategies that support the family's comprehension and decision-making processes. As it significantly influences the family's coping mechanisms, adherence to treatment, and overall psychological well-being. It is incumbent upon healthcare providers to approach this moment with a deep sense of responsibility and awareness of the numerous factors at play.

Modern medicine emphasizes the importance of informed consent and the patient's autonomy, albeit adapted for the pediatric context. This paradigm shift calls for a fine balance between providing information and support, facilitating understanding without overwhelming the caregivers emotionally (2).

Social workers, psychologists, and chaplains can provide support structures that extend beyond the immediate medical explanation (3). The involvement of an interdisciplinary team can be helpful in creating a supportive environment that accommodates the emotional, social, and spiritual needs of the family.

Moreover, the timing and setting of delivering such news cannot be overlooked. The original research (1) suggests that the impact of the news can be mitigated by ensuring that the setting is private, and the conversation is not rushed, allowing parents the time to process the information and ask questions (4). The use of clear, understandable language, free from medical jargon, further aids in this process.

While the focus is often on the initial delivery of the diagnosis, continuous communication is equally important. Follow-up meetings, consistent information about the child's status, and accessible language are part of ethical practice and care. A diagnosis is not a single event but a journey that the healthcare provider embarks upon with the family at the pace of child's condition progress. This often involves discussions around the goals of care, palliative options, and potentially end-of-life decisions—a trajectory that is challenging and delicate.

Finally, training and simulation in delivering difficult news have been shown to improve the confidence and skills of healthcare professionals (5). This kind of education is not just about the mechanics of communication but also about fostering empathy, patience, and the ability to read and respond to a family's emotional and non-verbal cues.

References

1. Karakaş Y. Current Approach to Reporting Bad News in Cancer Patients. Hitit Med J 2023;5(3): 227-231.
2. Ranmal R, Prictor M, Scott JT. Interventions for improving communication with children and adolescents about their cancer. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD002969.
3. Bluebond-Langner M, Belasco JB, Goldman A, Belasco C. Understanding parents' approaches to care and treatment of children with cancer when standard therapy has failed. J Clin Oncol Off J Am Soc Clin Oncol 2007 Jun 10;25(17):2414–9.
4. Mack JW, Joffe S. Communicating about prognosis: ethical responsibilities of pediatricians and parents. Pediatrics 2014 Feb;133 Suppl 1:S24-30.
5. Back AL, Arnold RM, Baile WF, et al. Efficacy of Communication Skills Training for Giving Bad News and Discussing Transitions to Palliative Care. Arch Intern Med 2007 Mar 12;167(5):453–60.

Response from the author:

(Karakaş Y. Current Approach to Reporting Bad News in Cancer Patients. Hitit Med J 2023;5(3): 227-231. https://doi.org/10.52827/hititmedj.1334284) Thank you for considering and clarifying this important issue. Giving bad news to pediatric patients and their relatives is a more difficult and complex issue. I think this letter, which evaluates this difficult process, will contribute to the readers.