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Antioksidanların Çift Yönlü Etkisi: Terapötik Potansiyel ve Paradoksal Roller

The Dual Action of Antioxidants: Therapeutic Potential and Paradoxical Roles

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ABSTRACT

Reactive oxygen species (ROS) play an important role in cancer pathogenesis. Normal cellular processes produce ROS, and these molecules promote tumor formation and genomic instability. However, ROS have a paradoxical effect: while high ROS levels promote cancer cell growth, excessive ROS accumulation can cause cancer cell death through oxidative stress. Cancer cells prevent oxidative damage by increasing their antioxidant capacity to maintain ROS balance, but this makes them vulnerable to treatment approaches that manipulate ROS. Strategies such as high-dose vitamin C have been shown to selectively induce death in cancer cells by increasing ROS. However, the use of antioxidants in cancer treatment is controversial. While reducing ROS may inhibit cancer cell growth, according to some researchers, excessive antioxidant intake may reduce the effectiveness of chemotherapeutic agents, as these drugs work by increasing ROS. As a result, antioxidants should be used with caution in cancer treatment, and a delicate balance should be maintained in ROS modulation strategies.

Keywords: *Oxidative stress, Antioxidant, Cancer*

ÖZET

Reaktif oksijen türleri (ROS), kanser patogenezinde önemli bir role sahiptir. Normal hücresel süreçler ROS üretir ve bu moleküller tümör oluşumu ile genomik instabiliteyi teşvik eder. Ancak, ROS'un paradoksal bir etkisi vardır: Yüksek ROS seviyeleri kanser hücresi büyümesini desteklerken, aşırı ROS birikimi oksidatif stres yoluyla kanser hücresi ölümüne neden olabilir. Kanser hücreleri, ROS dengesini korumak için antioksidan kapasitelerini artırarak oksidatif hasarı engeller, ancak bu durum onları ROS'u manipüle eden tedavi yaklaşımlarına karşı savunmasız hale getirir. Yüksek doz C vitamini gibi stratejilerin ROS'u artırarak kanser hücrelerinde seçici ölüm başlattığı gösterilmiştir. Bununla birlikte, antioksidanların kanser tedavisinde kullanımı tartışmalıdır. ROS'un azaltılması bazı araştırmacılara göre kanser hücresinin büyümesini engelleyebilirken, aşırı antioksidan alımı kemoterapötik ajanların etkinliğini düşürebilir, çünkü bu ilaçlar ROS'u yükselterek çalışır. Sonuç olarak, antioksidanlar kanser tedavisinde dikkatle ele alınmalı, ROS modülasyonu stratejilerinde hassas bir denge gözetilmelidir.

Anahtar kelimeler: *Oksidatif stres, Antioksidan, Kanser*

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Sayın Editör,

Zeynep Bozkoyun Dusak ve ark.'nın kaleme almış oldukları "Oksidatif Stres ve Kolorektal Kanser İlişkisinde Antioksidanların Önemli Rolü" isimli makaleyi (2024; 17(2):119-124) ilgiyle okudum. Makalede oksidatif stresin kanser oluşumundaki etkisine vurgu yapılmaktadır. Literatürde bu konuda yazılmış farklı bazı noktalara değinilmesinin konunun anlaşılmasına katkı sunacağına inanmaktayım. Bu mektupta, ilgili çalışmanın ortaya koyduğu bulgulara ek olarak, reaktif oksijen türlerinin (ROS) kanser gelişimi ve tedavisindeki ikili rolünü ele almakta ve bu bağlamda antioksidanların terapötik kullanımı konusundaki bilimsel tartışmalara katkı sağlamayı amaçlamaktayım.

Antioksidanların ve ROS'un kanser gelişimi ve tedavisindeki karmaşık rolü, onkoloji araştırmalarında oldukça tartışılan bir konu olmaya devam etmektedir. Normal hücresel reaksiyonlar yoluyla üretilen ROS, tümör oluşumunu ve genomik instabiliteyi teşvik ederek kanser patogenezine önemli ölçüde katkıda bulunur (Aggarwal ve ark., 2019). Ancak, ROS'un paradoksal doğası ikili işlevinde yatmaktadır: yüksek ROS seviyeleri kanser hücresi çoğalmasını teşvik ederken, aşırı ROS ayrıca oksidatif stres yoluyla kanser hücresi ölümünü de tetikleyebilir (Trachootham ve ark., 2006).

Kanser hücreleri, hayatta kalma arayışlarında, ROS homeostazını korumak için antioksidan kapasitelerini artırarak ölümcül oksidatif hasarı önler (Gorrini ve ark., 2013). Bu yetenek, kanser hücrelerini ROS seviyelerini manipüle eden stratejilere karşı daha savunmasız hale getirir. Çalışmalar, yüksek doz C vitamini gibi hedefli yaklaşımlarla ROS'u artırmanın, özellikle kolon kanseri modellerinde, kanser hücrelerinde seçici bir şekilde ölüme neden olabileceğini göstermiştir (Yun ve ark., 2015).

Bununla birlikte, antioksidanların kanser tedavisinde terapötik kullanımı tartışmalı olmaya devam etmektedir. Bazı araştırmacılar, ROS'u azaltmanın kanser hücresi çoğalmasını engelleyebileceğini öne sürerken, diğerleri aşırı antioksidan takviyesinin ROS üreten kemoterapötik ajanlarla etkileşime girebileceğini vurgulamaktadır (Schieber ve Chandel, 2014).

Birçok kemoterapik ajanın hücrelerde oksidatif stres oluşturarak etki gösterdiği bilinmektedir. Antioksidan takviyesinin ilgili ajanın etkinliğini azalttığına dair çalışmalar mevcuttur. Bu karmaşıklık, etkili terapötik stratejiler tasarlamada ROS modülasyonunda hassas bir dengenin olduğunu göstermektedir.

Antioksidan sistemin desteklenmesi kanserden korunma sürecinde rolü net bir şekilde anlaşılmakla birlikte kanser tedavisinde antioksidan sistemin rolü biraz daha karmaşık görünmektedir. Sonuç olarak, antioksidanlar hücresel homeostaziyi korumada önemli bir rol oynarken kanser tedavisinde terapötik uygulamaları, istenmeyen sonuçlardan kaçınmak için dikkatli bir şekilde ele alınmalıdır.

Çıkar Çatışması: Yazarın herhangi bir kurum veya kuruluş ile çıkar çatışması yoktur.

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Tıp, Diş Hekimliği ve Sağlık Bölümlerinde Okuyan Üniversite Öğrencilerinin Beslenme Alışkanlıklarının Diğer Bölümlerde Okuyan Öğrencilerin Beslenme Alışkanlıklarına Göre Değerlendirilmesi: Kesitsel Bir Çalışma

Evaluation of the Dietary Habits of University Students Studying in Medical, Dental, and Health Departments with Those of Students in Other Departments: A Cross-Sectional Study

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ABSTRACT

Objective: University is a period where individuals change their eating habits. The education provided influences individuals' nutrition and lifestyle patterns. This research aims to evaluate the eating habits of university students studying in different departments and examine the effects of their educational backgrounds on food consumption.

Material and Method: The study population consisted of students from Karabük University. Participation in the study was voluntary, and it was completed with 316 undergraduate and associate degree students. Research data were obtained through a questionnaire consisting of socio-demographic characteristics of students, their eating habits, and frequency of food consumption.

Results: Of the university students participating in the study, 75.3% were female and 24.7% were male. 10.1% of the participants were underweight, 63.9% were of normal weight, 20.9% were overweight, and 5.1% were obese. The highest normal Body Mass Index (BMI) value, with a rate of 49%, was observed among students studying in health-related fields. 67.1% of the participants consumed 2 main meals, with students studying in the Faculty of Engineering/Technology/Architecture/Technical Education having the highest rate (33.3%) of consuming 3 main meals. It was found that students studying in health-related fields were the most attentive to healthy eating habits, with 26.3% reporting their attention to it. The frequency of consuming protein-rich foods is higher among students studying in health-related fields compared to other departments. The frequency of carbohydrate-rich food consumption is higher among students in other fields. Similarly, it was observed that the frequency of consuming snacks is lower among students studying in health-related faculties compared to students in other faculties.

Conclusion: Students studying in health-related departments appear to be more sensitive and attentive to nutrition compared to students in other departments. Therefore, providing courses related to nutrition and health in universities, increasing educational activities, and fostering a culture of healthy eating will contribute to the promotion of healthy nutrition.

Keywords: *Nutrition, Eating habits, University students*

ÖZET

Giriş: Üniversite bireyin beslenme alışkanlıklarının değişikliğe uğradığı bir dönemdir. Verilen eğitimler bireyin beslenme ve yaşam modelini etkiler. Bu araştırmada, farklı bölümlerde okuyan üniversite öğrencilerinin beslenme alışkanlıklarını değerlendirmek ve eğitim gördükleri bölümlerin besin tüketimleri üzerine etkilerini incelemek amaçlamıştır.

Materyal ve Metot: Araştırma evrenini Karabük Üniversitesi öğrencileri oluşturmaktadır. Araştırmaya katılmak gönüllük esasına dayanmaktadır ve araştırma örgün eğitim gören 316 lisans ve ön lisans öğrencisi ile tamamlanmıştır. Araştırma verileri öğrencilerin sosyo-demografik özellikleri, beslenme alışkanlıkları ve besin tüketim sıklığı formu sorularından oluşan bir anket ile elde edilmiştir.

Bulgular: Araştırmaya katılan üniversite öğrencilerinin %75,3'i kız, %24,7'si erkektir. Katılımcıların %10,1'inin zayıf, %63,9'unun normal, %20,9'unun fazla kilolu, %5,1'inin ise obezdir. %49 oranı ile en yüksek normal Beden Kitle İndeksi (BKİ) değeri sağlık alanlarında eğitim gören öğrencilerde görülmüştür. Katılımcıların %67,1'inin (en yüksek oran) 2 ana öğün tükettiği, 3 ana öğün tüketiminin ise %33,3 (en fazla) oranı ile Mühendislik/Teknoloji/Mimarlık/Teknik Eğitim Fakültesinde eğitim alan öğrenciler olduğu bulunmuştur. Sağlıklı beslenmeye en fazla (%26,3) sağlık bölümlerinde eğitim gören öğrencilerin dikkat ettiklerini bildirdikleri görülmektedir. Protein ağırlıklı besin tüketim sıklığı sağlık alanlarında eğitim gören öğrencilerde diğer bölümlere göre daha yüksektir. Karbonhidratlı besin tüketim sıklığı ise diğer alanlarda eğitim gören öğrencilerde daha yüksektir. Benzer şekilde sağlıkla ilgili fakültelerde eğitim gören öğrencilerin abur cubur tüketim sıklıklarının diğer fakültelerdeki öğrencilere göre daha az olduğu gözlenmiştir.
Sonuç: Sağlık bölümlerinde eğitim gören öğrencilerin diğer bölümlerde eğitim gören öğrencilere göre beslenme konusunda daha duyarlı ve dikkatli oldukları görülmektedir. Bu nedenle üniversitelerde beslenmenin sağlık ile ilgisini içeren derslerin verilmesi, eğitimlerin arttırılması, sağlıklı beslenme kültürünün oluşturulmasına katkı sağlayacaktır.

Anahtar kelimeler: *Beslenme, beslenme alışkanlıkları, üniversite öğrencileri*

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GİRİŞ

Günümüzün en önemli sorunu haline gelen kronik bulaşıcı olmayan hastalıkların sık görülmesinin en önemli sebepleri, sağlıksız beslenme, fiziksel aktivite yetersizliği, sigara ve alkol tüketimi, yanlış beslenme alışkanlıklarıdır. Yaşam tarzındaki değişiklik ve düzeltmeler ile Bulaşıcı Olmayan Hastalık (BOH))'ların önlenmesi mümkündür (Dolatkhan ve ark., 2019; Arosio ve Cesari, 2021). Toplumdaki sağlık yükünün büyük çoğunluğu sağlıksız beslenme, sigara tüketimi ve sedanter yaşam gibi değiştirilebilir davranışlardan ileri gelmektedir. Gerekli sağlık bilgilendirmeleri ve düzenlemeleri ile öz denetimler yapılmaktadır. Böylece toplumda daha sağlıklı yaşam tarzlarına yöneltme ve dolaylı yollardan bulaşıcı olmayan hastalıkların seyrinin azaltılması desteklenmektedir (Bucher ve ark., 2016).

Üniversite, öğrencilerin yaşam tarzı alışkanlıklarındaki değişikliklerin meydana geldiği ve bu farklılığın ilerleyen yıllardaki yetişkinlik dönemine kadar ilerleyebildiği ve bu nedenle sağlığı etkileyebildiği önemli bir süreçtir. Birçok araştırmacı, üniversite öğrencileri arasında fast food ve yüksek yağlı yiyeceklerin tüketiminin artması gibi sağlıksız beslenme uygulamalarının üniversite öğrencilerinde daha fazla olduğu bildirmiştir (Yılmaz ve Özkan, 2007; El Ansari ve ark., 2012). Önde gelen halk sağlığı ve eğitim ortakları bireylerin bilgi, tutum ve beslenme de dahil olmak üzere çok çeşitli alanlarda gençlerin sağlık davranışları ve deneyimlerini ele almak için okul sağlığı eğitiminin önemini vurgulamakta ve sağlık eğitiminin öğrenci sağlığı ve akademik yaşam üzerindeki rolünü ve etkisini incelemek için ek çalışmalar yapılması çağrısında bulunmaktadır (Lee ve ark., 2023).

Bu araştırma farklı bölümlerde eğitim alan üniversite öğrencilerinin beslenme bilgi, tutum ve alışkanlıklarını değerlendirmek, karşılaştırmak ve sağlık alanlarında eğitim alan öğrencilerin aldıkları eğitimin beslenme durumları ve alışkanlıklarına etkisini incelemek amacıyla gerçekleştirilmiştir.

MATERYAL ve METOT

Bu araştırma tanımlayıcı, kesitsel türde bir çalışmadır. Araştırma kapsamında Karabük Üniversitesinde farklı bölümlerde eğitim gören öğrencilerin beslenme alışkanlıkları ve besin tüketim sıklıkları değerlendirilmiştir. Araştırmanın evrenini Karabük Üniversitesi oluşturmaktadır. Yüksek Öğretim Kurumu (YÖK) 2022-2023 verilerine göre Karabük Üniversitesine kayıtlı ön lisans ve lisans olmak üzere toplam öğrenci sayısı 40259'dur (YÖK, 2023). Örneklem büyüklüğü %95 güven aralığında ve %5 hata payı oranına göre en az 333 olarak öngörülmüştür (Yazıcıoğlu ve Erdoğan, 2014). Farklı bir kaynakta da 3000 kişilik evren aralığında yeterli örneklem büyüklüğünün 341 kişi olduğu ifadesi bulunmaktadır (Sekaran, 1992). Bu veriler ışığında örneklem sayısı 350 kişi olarak planlanmıştır. Fakat araştırmaya katılma gönüllülük esasına dayanması sebebiyle ve hatalı verilerin elenmesi sebebiyle 316 kişi ile araştırma tamamlanmıştır. Araştırma verileri Aralık 2023 ile Ocak 2024 tarihleri arasında toplanmıştır. Araştırmaya beslenme ve besin tercihi farklılık göstereceği için yabancı uyruklu öğrenciler dahil edilmemiştir. Katılımcılara gönüllü onam formu ve araştırma anket formu (27 soru) çevrimiçi olarak uygulanmıştır. Anket soruları literatürdeki kaynaklardan faydalanarak oluşturulmuştur (Saygın ve ark. 2011; Ermiş ve ark., 2015; Onurlubaş ve ark., 2015; Arslan ve ark. 2016). Anket formu iki bölümden oluşmaktadır; birinci bölümünde bireylerin demografik özellikleri (yaş, cinsiyet, antropometrik ölçümler gibi), ikinci bölümünde beslenme alışkanlıkları ve tüketim sıklıkları yer almaktadır. Bireylerin antropometrik ölçümleri (boy ve ağırlık) Dünya Sağlık Örgütü (WHO) BKİ (Beden kitle indeksi) verilerine göre zayıf (<18,5 kg/m^2), normal (18,5-24,9 kg/m^2), fazla kilolu (25,0-29,9 kg/m^2) ve obez (>30,0 kg/m^2) olarak sınıflandırılmıştır (WHO, 2010). Çalışma araştırma ve yayın etiğine uygun olarak yürütülmüştür.

İstatistiksel Analiz

Araştırma sonucunda elde edilen veriler SPSS 23.0 paket programından yararlanılarak değerlendirilmiştir. Araştırmada değişken olarak öğrencilerin eğitim gördüğü fakülteler kullanılmıştır. Araştırma verileri sayı ve yüzde (%) değerler ile tablolar halinde gösterilmiştir. Birden fazla seçenek yanıtlanan sorulara ilişkin yüzde değerler her bir seçenek için "n" sayısı dikkate alınarak hesaplanmıştır. Sosyo-demografik özelliklerin değerlendirilmesinde Frekans Analizi uygulanmıştır. Öğrencilerin eğitim gördüğü fakültelerin öğün sayısı, öğün atlama durumları, beslenme eğitim durumları, beslenme alışkanlıkları, BKİ değerlendirilmesi, sağlıklı beslenme durumları Ki-Kare testi ile değerlendirilmiştir.

BULGULAR

Çalışmaya 316 üniversite öğrencisi katılmış olup bunların sosyo-demografik özellikleri Tablo 1'de gösterilmektedir.

Tablo 1. Öğrencilerin sosyo-demografik özellikleri

		Sayı (n)	Yüzde (%)
Cinsiyet	Kız	238	75,3
	Erkek	78	24,7
Yaş (yıl)	19 yaş altı	61	19,3
	19-25 yaş	239	75,6
	25 yaş üstü	16	5,1
Eğitim düzeyi	Ön lisans	71	22,5
	Lisans	245	77,5
Eğitim aldığınız fakülte	Tıp / Diş hekimliği/Sağlık Bilimleri Fakültesi / Sağlık Hizmetleri Yüksekokulu	144	45,6
	İBF / İşletme / İletişim / Güzel Sanatlar / Turizm Fakültesi	77	24,4
	Mühendislik / Teknoloji / Mimarlık / Teknik Eğitim Fakültesi	15	4,7
	Edebiyat / Fen / İslami İlimler Fakültesi	37	11,7
	Meslek Yüksekokulları (diğer)	43	13,6
Öğrenim gördüğünüz sınıf	1. Sınıf	167	52,8
	2. Sınıf	59	18,7
	3. Sınıf	27	8,5
	4. Sınıf	60	19,0
	5. Sınıf	1	0,3
	6. Sınıf	2	0,6
Kaldığınız yer	Aile ile evde	71	22,5
	Yurtta	188	59,5
	Arkadaşlar ile evde	32	10,1
	Evde tek başına	25	7,9
Sigara içme durumu	Evet	70	22,2
	Hayır	246	77,8
Düzenli alkol kullanımı	Evet	22	7,0
	Hayır	294	93,0
Toplam		316	100,0

Bireylerin beslenme alışkanlıkları incelendiğinde; %67,1'inin (en yüksek oran) 2 ana öğün, %26,8'inin 3 ana öğün ve %6,0'ının 1 ana öğün yaptığı görülmektedir. 3 ana öğün tüketimi %33,3 (en fazla) ile Mühendislik/Teknoloji/Mimarlık/Teknik Eğitim Fakültesi öğrencileridir. Bu değeri %29,9 ile sağlık alanlarında eğitim alan öğrenciler takip etmektedir. 3 ana öğün tüketimini en az yapanlar %20,9 oranı ile diğer meslek yüksekokullarında okuyan öğrencilerdir. Tüm bölümlerdeki öğrencilerin çoğunluğu gün içerisinde 1 ara öğün tükettiğini bildirmiştir. Günde 1 ara öğün tüketen öğrencilerin %67,4'ü (en fazla) diğer meslek yüksekokulu öğrencileridir (Tablo 2).

Tablo 2. Bireylerin ana ve ara öğün tüketim durumları

Eğitim alanı	Günde kaç ana öğün beslenirsiniz?							
	1		2		3		Toplam	
	N	%	N	%	N	%	N	%
Tıp / Diş hekimliği/Sağlık Bilimleri Fakültesi/Sağlık Hizmetleri Yüksekokulu	4	2,8	97	67,3	43	29,9	144	100
İBF/İşletme/İletişim/Güzel Sanatlar/Turizm Fakültesi	4	5,1	53	68,8	20	25,9	77	100
Mühendislik/Teknoloji/Mimarlık/Teknik Eğitim Fakültesi	1	6,6	9	60,0	5	33,3	15	100
Edebiyat/Fen/İslami İlimler Fakültesi	3	9,1	26	70,2	8	21,6	37	100
Meslek Yüksekokulları (diğer)	7	16,2	27	62,7	9	20,9	43	100
Toplam	19	6,0	212	67,1	85	26,8	316	100
	Günde kaç ara öğün beslenirsiniz?							
	1		2		3		Toplam	
	N	%	N	%	N	%	N	%
Tıp / Diş hekimliği/Sağlık Bilimleri Fakültesi/Sağlık Hizmetleri Yüksekokulu	72	50,0	55	38,2	17	11,8	144	100
İBF/İşletme/İletişim/Güzel Sanatlar/Turizm Fakültesi	41	53,2	27	35,0	9	11,6	77	100
Mühendislik/Teknoloji/Mimarlık/Teknik Eğitim Fakültesi	5	33,3	5	33,3	5	33,3	15	100
Edebiyat/Fen/İslami İlimler Fakültesi	24	64,8	10	27,0	3	8,1	37	100
Meslek Yüksekokulları (diğer)	29	67,4	9	20,9	5	11,6	43	100
Toplam	171	54,1	106	33,5	39	12,3	316	100

Üniversite öğrencilerinin sağlıklı beslenmeye dikkat etme durumları incelendiğinde %45,6'sı evet, %54,4'ü hayır yanıtını vermiştir. Sağlıklı beslenmeye en fazla (%26,3) sağlık bölümlerinde eğitim gören öğrencilerin dikkat ettiklerini bildirdikleri görülmektedir. Katılımcıların %12,7'si öğün atlamazken %46,2'si en çok öğle öğününü atladıklarını bildirmiştir. Sabah öğününü atlayan öğrenciler %26,3 iken akşam öğününü atlayan öğrenci oranı %4,4 olarak tespit edilmiştir. Öğrencilerin en çok atladığı ara öğünler sırayla; kuşluk (%25,6), ikindi (%20,6), gece (%16,1) olarak belirlenmiştir. Bireylerin öğün atlama nedenleri incelendiğinde; %35,8'i acıkmamak, %31,0'ı unutmak/zaman ayıramamak, %15,5'i ekonomik yetersizlik, %13,6'sı sabah uyanamamak, %5,7'si ise kilo vermek nedeniyle öğün atladıklarını bildirmiştir (Tablo 3).

Tablo 3. Bireylerin sağlıklı beslenmeye dikkat etme, öğün atlama durumu ve nedenleri

		Eğitim gördüğü fakülte					**Total**	
		Tıp/Diş hekimliği/Sağlık Bilimleri Fakültesi/Sağlık Hizmetleri Yüksekokulu	İBF/İşletme / İletişim/Güzel Sanatlar/Turizm Fakültesi	Mühendislik /Teknoloji /Mimarlık/ Teknik Eğitim Fakültesi	Edebiyat /Fen/İslami İlimler Fakültesi	Meslek Yüksekokulları (diğer)	**N**	**%**
Sağlıklı beslenmeye dikkat etme durumu	Evet	83	28	9	11	13	**144**	**45,5**
	Hayır	61	49	6	26	30	**172**	**54,5**
	Toplam	**144**	**77**	**15**	**37**	**43**	**316**	
Atlanan öğün hangisidir? *	Atlamam	14	7	7	3	9	**40**	**8,3**
	Sabah	30	22	5	13	13	**83**	**17,2**
	Öğle	59	38	5	23	21	**146**	**30,4**
	Akşam	6	4	0	1	3	**14**	**2,9**
	Kuşluk	34	21	3	10	13	**81**	**16,8**
	İkindi	34	13	3	7	8	**65**	**13,5**
	Gece	23	16	2	6	4	**51**	**10,6**
	Toplam	**200**	**121**	**25**	**63**	**71**	**480**	
Öğün atlama nedeni nedir?*	Yok	11	9	3	4	7	**34**	**9,5**
	Sabah uyanamama k	18	10	1	10	4	**43**	**12,1**
	Kilo vermek için	8	3	0	2	5	**18**	**5,0**
	Unutmak /zaman ayıramamak	46	24	3	14	11	**98**	**27,6**
	Acıkmamak	68	24	6	8	7	**113**	**31,8**
	Ekonomik yetersizlik	11	13	2	8	15	**49**	**13,8**
	Toplam	**162**	**83**	**15**	**46**	**49**	**355**	

*Birden fazla seçenek işaretlenmiştir.

Bireylerin BKİ sınıflandırması değerlendirildiğinde; en yüksek oranda normal BKİ dağılımına sahip olan bireyler sağlık alanları eğitim görenlerdir alanlar (%49,0). Obez öğrencilerin ise en fazla oranda (%50,0) İBF/İşletme/İletişim/Güzel Sanatlar/ Turizm Fakültesi'nde eğitim görenler olduğu bulunmuştur (Tablo 4).

Tablo 4. Bireylerin BKİ Dağılımları

		BKİ Sınıflandırma					
Eğitim Alanı		**Zayıf**	**Normal**	**Fazla kilolu**	**Obez**	**Total**	***p**
Tıp/Diş hekimliği/Sağlık Bilimleri Fakültesi/Sağlık Hizmetleri Yüksekokulu	N	15	103	22	4	144	0,03
	%	46,9	49,0	30,3	25,0	45,6	
İBF/İşletme/İletişim/Güzel Sanatlar/Turizm Fakültesi	N	10	36	23	8	77	
	%	31,3	17,8	34,8	50,0	24,4	
Mühendislik/Teknoloji/Mimarlık/Teknik Eğitim Fakültesi	N	0	10	4	1	15	
	%	0,0	5,0	6,1	6,3	4,7	
Edebiyat/Fen/İslami İlimler Fakültesi	N	5	21	10	1	37	
	%	15,6	10,4	15,2	6,3	11,7	
Meslek Yüksekokulları (diğer)	N	2	32	7	2	43	
	%	6,3	15,8	10,6	12,5	13,6	
Toplam	N	32	202	202	66	16	
	%	100,0	100,0	100,0	100,0	100,0	

*Ki-Kare Testi

Katılımcıların protein ağırlıklı besinleri tüketim sıklık durumları değerlendirildiğinde; sağlık alanlarında eğitim gören öğrenciler ile diğer alanlarda eğitim gören öğrencilerin protein içerikli besinleri tüketme sıklıkları birbirine benzer olarak görülmektedir. Günlük tercihler değerlendirildiğinde; peynir ve kurubaklagil ürünlerini sağlık alanında eğitim gören öğrencilerin daha fazla tercih ettikleri (%15,1 ve %3,5) fakat süt, yumurta, beyaz et ve balık tüketiminin ise diğer alanlarda eğitim gören öğrencilerde daha fazla tercih edildiği görülmektedir (Tablo 5).

Tablo 5. Bireylerin protein içerikli besinleri tüketim dağılımları

Ürün	**Eğitim alanı**	**Her gün**		**Haftada 5-6 kez**		**Haftada 3-4 kez**		**Haftada 1-2 kez**		**15 günde 1 kez**		**Ayda 1 kez**		**Hiç**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Süt	**Sağlık**	5	1,6	13	4,1	14	4,4	46	14,5	25	7,9	14	4,4	27	8,5
	Diğer	11	3,5	9	2,8	24	7,6	37	11,7	21	6,6	35	11,0	35	11,0
Peynir	**Sağlık**	48	15,1	29	9,2	30	9,5	22	6,9	5	1,6	4	1,3	6	1,9
	Diğer	52	7,9	17	5,4	49	15,5	30	9,5	7	2,2	5	1,6	12	3,8
Yumurta	**Sağlık**	18	5,7	18	5,7	33	10,4	42	13,2	12	3,8	10	3,1	11	3,5
	Diğer	26	8,2	20	6,3	42	13,3	38	12,0	8	2,5	18	5,7	20	6,3
Kurubaklagil	**Sağlık**	11	3,5	12	3,8	31	9,8	40	12,6	26	8,2	9	2,8	15	4,7
	Diğer	10	3,1	16	5,0	40	12,6	53	16,8	22	6,9	8	2,5	23	7,3
Kırmızı et	**Sağlık**	3	0,9	9	2,8	22	6,9	61	19,3	22	6,9	13	4,1	14	4,4
	Diğer	3	0,9	11	3,5	30	9,5	40	12,6	35	11,0	32	10,1	21	6,6
Beyaz et	**Sağlık**	7	2,2	13	4,1	33	10,4	59	18,7	15	4,7	8	2,5	9	2,8
	Diğer	9	2,8	13	4,1	49	15,5	43	13,6	26	8,2	17	5,4	15	4,7
Balık	**Sağlık**	3	0,9	4	1,2	6	1,9	18	5,7	36	11,4	42	13,3	35	11,0
	Diğer	4	1,2	6	1,9	14	4,4	16	5,0	32	10,1	53	16,8	47	14,9

Katılımcıların protein ağırlıklı besinleri tüketim sıklık durumları değerlendirildiğinde; eğitim gördükleri fakültelere göre peynir, kırmızı et ve beyaz et besinleri tüketme sıklıkları arasında pozitif anlamlı bir korelasyon olduğu görülmektedir ($p<0.01$) (Tablo 7). Ayrıca tüm protein içerikli besinlerin tüketim sıklık durumlarının birbirleri ile pozitif ve anlamlı ilişkileri olduğu görülmektedir ($p<0.01$). Örneğin bireylerin süt tüketim sıklığı peynir, yumurta, kuru baklagil, kırmızı et ve beyaz et tüketim sıklıkları ile pozitif ve anlamlı olarak ilişkilidir ($p<0.01$), sadece balık tüketim sıklığını etkilememektedir. Bireylerin balık tüketim sıklıklarını yumurta, kuru baklagil, kırmızı et ve beyaz et tüketim sıklıkları etkilemektedir ($p<0.01$).

Tablo 6. Bireylerin protein içerikli besinleri tüketim durumlarının eğitim alanları ile korelasyonu

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Eğitim Görülen Fakülte[1]	1							
Süt[2]	0,094	1						
Peynir[3]	,152**	,188**	1					
Yumurta[4]	0,103	,287**	,293**	1				
Kuru baklagil[5]	0,073	,161**	,311**	,168**	1			
Kırmızı et[6]	,165**	,159**	,151**	,266**	,397**	1		
Beyaz et[7]	,164**	,209**	,174**	,278**	,384**	,579**	1	
Balık[8]	-0,03	0,091	0,097	,156**	,260**	,415**	,420**	1

** $p<0.01$.

Katılımcıların diğer besinleri tüketim sıklıkları incelendiğinde sağlık bölümlerinde okuyan öğrencilere göre diğer bölümlerde okuyan öğrencilerin daha sık karbonhidrat ağırlıklı besinleri tükettikleri (örneğin; ekmek her gün %34,2, simit-poğaça her gün %4,1, tahıl ürünleri her gün %14,5) ve sağlık alanlarında okuyan öğrencilerin diğer bölümlerde okuyan öğrencilere göre daha sık meyve tükettikleri (her gün %15,5) görülmektedir (Tablo 7).

Tablo 7. Bireylerin diğer besinleri tüketim dağılımları

Ürün	**Eğitim alanı**	**Her gün**		**Haftada 5-6 kez**		**Haftada 3-4 kez**		**Haftada 1-2 kez**		**15 günde 1 kez**		**Ayda 1 kez**		**Hiç**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Ekmek	**Sağlık**	85	26,9	22	6,9	13	4,1	10	3,1	2	0,6	4	1,2	8	2,4
	Diğer	108	34,2	23	7,3	18	5,7	11	3,5	6	1,9	4	1,2	3	0,9
Simit-poğaça	**Sağlık**	5	1,5	5	1,5	22	6,7	56	17,7	28	8,8	21	6,6	7	2,2
	Diğer	13	4,1	12	3,8	30	9,5	60	18,9	20	6,3	19	6,0	18	5,7
Tost-sandviç	**Sağlık**	10	3,1	13	4,1	29	9,1	30	9,5	32	10,1	16	5,0	14	4,4
	Diğer	13	4,1	8	2,4	33	10,4	42	13,3	35	11,0	18	5,7	23	7,3
Kahvaltılık gevrekler	**Sağlık**	4	1,2	4	1,2	16	5,0	19	6,0	15	4,7	23	7,3	62	19,6
	Diğer	7	2,2	13	4,1	22	6,7	19	6,0	14	4,4	26	8,2	71	22,5
Tahıl ürünleri	**Sağlık**	38	12,0	37	11,7	33	10,4	20	6,3	7	2,2	3	0,9	6	1,8
	Diğer	46	14,5	41	12,9	47	14,9	24	7,6	10	3,1	4	1,2	0	0
Bal/reçel/pekmez	**Sağlık**	11	3,5	10	3,1	29	9,2	40	12,6	22	6,9	11	3,5	21	6,6
	Diğer	15	4,7	17	5,4	34	10,8	36	11,4	13	4,1	23	7,3	34	10,7
Sebzeler	**Sağlık**	31	9,8	22	6,9	34	10,8	32	10,1	14	4,4	8	2,4	3	0,9
	Diğer	35	11,1	29	9,2	47	14,9	34	10,7	15	4,7	5	1,5	7	2,2
Meyveler	**Sağlık**	49	15,5	25	7,9	34	10,8	24	7,6	6	1,9	3	0,9	3	0,9
	Diğer	42	13,3	32	10,1	42	13,3	21	6,6	18	5,7	7	2,2	10	3,1

Katılımcıların diğer besinleri tüketim sıklıkları incelendiğinde eğitim aldıkları bölümlere göre meyve tüketim sıklıklarında pozitif anlamlı bir korelasyon olduğu görülmektedir ($p<0.01$) (Tablo 8). Bu veriler dışında tost/sandviç tüketim sıklıkları ile simit-poğaça tüketim sıkları arasında; kahvaltılık gevreklerin tüketim sıklıkları ile simit-poğaça ve tost/sandviç tüketim sıklıkları arasında; tahıl ürünleri tüketim sıklıkları ile ekmek tüketim sıklıkları arasında; bal/reçel/pekmez tüketim sıklıkları ile ekmek, simit-poğaça ve tost/sandviç tüketim sıklıkları arasında; sebze tüketim sıklıkları ile ekmek ve tahıl ürünleri tüketim sıklıkları arasında; meyve tüketim sıklıkları ile ekmek, simit-poğaça, tost/sandviç ($p<0.05$), tahıl ürünleri ve sebze tüketim sıklıkları arasında anlamlı pozitif bir korelasyon olduğu görülmektedir ($p<0.01$) (Tablo 8).

Tablo 8. Bireylerin diğer besinleri tüketim durumlarının eğitim alanları ile korelasyonu

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Eğitim görülen fakülte[1]	1								
Ekmek[2]	-0,045	1							
Simit, poğaça[3]	-0,109	0,066	1						
Tost/sandviç[4]	-0,03	0,027	,510**	1					
Kahvaltılık Gevrekler[5]	-0,086	-0,04	,168**	,246**	1				
Tahıl ürünleri[6]	-0,011	,227**	0,046	0,048	0,088	1			
Bal/reçel/pekmez[7]	0,025	,170**	,281**	,163**	0,071	0,103	1		
Sebzeler[8]	0,019	,195**	-0	0,021	0,093	,511**	0,066	1	
Meyveler[9]	,188**	,135*	,154**	,111*	0,068	,359**	,163**	,503**	1

** $p<0.01$. * $p<0.05$.

TARTIŞMA

Öğrencilik süreci, bireylerin kendi tercihlerine göre yaşam tarzlarına yön verdikleri zamandır (Deshpande ve ark., 2009). Ülkemizde yapılan çalışmalar incelendiğinde üniversite öğrencilerinde öğün atlama durumlarının sıklığının fazla olduğu, süt grubu ürünlerinin önerilenden daha az tüketildiği, fast food tüketiminin sık olduğu görülmektedir (Arslan ve Mendeş, 2004; Özdoğan ve ark., 2012; Sayılı ve Gözener, 2013). Araştırmaya katılan bireylerin beslenme alışkanlıkları değerlendirildiğinde; katılımcıların %91'inin öğün atladığı ve %26,8'inin günde 3 ana öğün ile beslendiğini bulunmuştur (Tablo 2). Bu sonuçlar yapılan çalışmalar ile benzerlik göstermektedir (Rampersaud ve ark., 2005; Yaman ve Yabancy, 2006). Farklı çalışmalarda öğrencilerin %60-70'inin günde 3 ana öğün beslendiği bildirilmiştir (Vançelik ve ark., 2007; Rosalino ve ark., 2013). Fakat bu çalışmada öğrencilerin 3 öğün tüketim oranı diğer çalışmalara göre daha az bulunmuştur.

Yapılan bir çalışmada öğrencilerin en çok atladığı öğünün sabah kahvaltısı olduğu belirtilmiştir (Önay, 2011). Benzer şekilde yapılan çalışmalarda en sık atlanan öğün kahvaltı öğünü olduğu görülmüştür (Nola ve ark., 2010; Oluk ve Oluk, 2011).

Yapılan bu çalışmada ise en sık atlanan öğünün %46,2 ile öğle öğünü olduğu, 2. sırada ise %26,3 ile sabah kahvaltısı olduğu bulunmuştur. Çalışma sonuçları diğer çalışmalar ile farklılık göstermektedir. Fakat Erten'in 2006 yılında yaptığı çalışma bu çalışma ile benzerlik göstermektedir (Erten, 2006).

Çalışmada öğün atlama nedenleri incelendiğinde %35,8'i aç olmama, %31,0'ı unutma/zaman bulamama, 15,5'i ekonomik yetersizlik, %13,6'sı sabah uyanamama, %5,7'si ise kilo verme olarak bildirilmiştir. Yapılan farklı çalışmalarda ise öğün atlamanın en sık nedeni unutma veya fırsat bulamama olarak belirtilmektedir (Açık ve ark, 2003; Vançelik ve ark., 2007).

Yapılan bu çalışmada sağlıklı beslenmeye dikkat eden öğrencilerin %26,3'ünün (en fazla) sağlık bölümlerinde eğitim gören öğrencilerden oluştuğu saptanmıştır. Kim ve Kim tarafından yapılan bir çalışmada, hemşirelik öğrencilerinin beslenme bilgi düzeyleri ile beslenme tutumlarının doğru orantılı etki gösterdiği bildirilmiştir (Kim ve Kim, 2015). Hemşirelik, hukuk ve İslami ilimler bölümlerinde okuyan 905 üniversite öğrencisi üzerinde yapılan geniş çaptaki çalışmada, sağlık okuryazarlığının beslenme bilgisi ile bağlantılı olduğu belirlenmiştir (Uysal ve ark., 2020).

Yapılan bu çalışmada öğrencilerin BKİ değerleri incelendiğinde; %10,1'i zayıf, %63,9'u normal, %20,9'u fazla kilolu, %5,1'i obez olarak saptanmıştır. Ayrıca sağlık bölümlerinde okuyan öğrencilerin %49'unun (en yüksek oran) normal BKİ değerlerinde olduğu bulunmuştur. Yapılan başka bir çalışmaya göre obez ya da fazla kilolu prevalansı %12,8 olurken (Haq ve ark., 2018), Çinli tıp öğrencilerinin obezite ya da fazla kilolu prevalansının ise daha düşük olduğu belirtilmiştir (Sakamaki ve ark., 2005). Yapılan çalışmalarda toplumu daha sağlıklı beslenme alışkanlıklarına yöneltmek ve bulaşıcı olmayan kronik hastalıkları ile ilgili kişisel bakımı geliştirmek için toplumun gıda ve beslenme konusunda bilgilenmesi büyük önem taşıdığı görülmüştür (Triches ve ark., 2005; Pereira ve ark., 2012).

Yapılan çalışmalarda üniversite öğrencilerinin daha fazla fastfood türü hızlı besin kaynaklarını tükettikleri belirtilmektedir (Işkın ve Sarıışık, 2017; Sacko ve Arslan, 2022). Literatür tarandığında sağlık alanlarında eğitim alan öğrenciler ile diğer alanlarda eğitim alan öğrencilerin besin tüketimlerini karşılaştıran çalışmalar mevcut değildir. Fakat genel yapılan çalışmalara bakıldığında; öğrencilerin %48,6'sı kahvaltıda simit, ekmek tükettiklerini, %6,3'ünün tost, sandviç tükettiklerini, %1,1'inin kahvaltılık gevrek tükettiklerini belirttikleri bildirilmektedir (Yılmaz ve Özkan, 2007). Bu çalışmada ise öğrencilerin simit-poğaça tüketimleri incelendiğinde sağlık alanlarında eğitim görenlerin %1,5'i, diğer alanlarda eğitim görenlerin %4,1'i her gün tükettiklerini; tost-sandviç tüketimleri incelendiğinde ise sağlık alanlarında eğitim gören öğrencilerin %3,1'i, diğer alanlarda eğitim gören öğrencilerin ise %4,1'i her gün tost-sandviç tükettiklerini belirtmişlerdir. Genel olarak sağlık alanlarında eğitim gören öğrencilerin daha sağlıklı besinleri tercih ettikleri söylenebilir.

Dört faklı ülke (Bulgaristan, Almanya, Polonya) öğrencileri üzerine yapılan bir çalışmada et tüketimleri incelendiğinde, sık et tüketimi tüm ülkelerde nispeten yüksek olarak bildirilmiştir (%44-%53 arasında değişmektedir). Yüksek sıklıkta balık tüketimini ise en çok Bulgar öğrencilerin tükettiği belirtilmiştir (El Ansari ve ark., 2012). Yapılan bu çalışmada ise tüm et türlerinin tüketimi hem sağlık alanlarında hem de diğer alanlarda eğitim alan öğrencilerde düşük olarak bulunmuştur. Bu çalışmada karbonhidrat oranı yüksek olan besinlerin her iki grup içinde tüketiminin protein içerikli besinlere göre daha fazla olduğu söylenebilir (Tablo 7). Bu sonuçlar protein içeriği yüksek olan et ve et ürünlerinin maddi açıdan değerlendirildiğinde karbonhidratlı ürünlere göre daha pahalı olmasından kaynaklı olabilir. İleriki çalışmalarda öğrencilerin besin tüketim durumlarının daha fazla netlik kazanması için tüketilen besinlerin sıklıkları ile beraber tüketim miktarlarının da sorgulanması literatüre katkı sağlayacaktır.

Sonuç

Yapılan bu araştırmada sağlık alanlarında eğitim alan öğrencilerin diğer alanlarda eğitim alan öğrencilere göre BKİ değerlerinin daha düşük olduğu ve sağlıklı beslenmeye daha fazla dikkat ettikleri görülmüştür. Karbonhidrat ağırlıklı besin tüketim sıklığının diğer alanlarda eğitim gören öğrencilerde daha fazla olduğu bulunmuştur. Fakat genel olarak hem sağlık alanlarında hem de diğer alanlarda eğitim gören öğrencilerin protein ağırlıklı besinleri daha az tükettikleri sonucuna ulaşılmıştır. Bu durum üniversite eğitimi sırasında öğrencilerin yaşadıkları ekonomik yetersizlerden de kaynaklıyor olabilmektedir. Bu durum üniversite öğrencilerinin sağlıksız beslenme alışkanlığının değerlendirilmesinin ve erken zamanda belirlenmesinin ciddi bir toplumsal ihtiyaç haline geldiğini gün yüzüne çıkarmaktadır. Sağlığın korunması ve geliştirilmesinde beslenme bilgisinin yeterli olması en önemli kriterdir. Bu nedenle öğrenciler başta olmak üzere topluma beslenme eğitimlerinin düzenli olarak verilmesi toplum bilincinin artırılmasına katkı sağlayacaktır. Sürdürülebilir sağlık modeli için genç nesillerin beslenme konularında eğitilmelerinin desteklenmesi gerekmektedir. İleriki çalışmalarda üniversite öğrencilerinin besin tüketim sıklıkları ile tüketim miktarlarının da sorgulanması, besin tercihlerini etkileyen olası durumlarının da irdelenmesi bu dönem bireylerin besin tüketim alışkanlıklarının belirlenmesinde daha faydacı bir yaklaşım sağlayacaktır. Ayrıca besin tercihlerini etkileyen olası kriterler de belirlenerek bu grup bireylerin beslenme modellerinin iyileştirilmesinde daha etkili yaklaşımların belirlenmesini sağlayacaktır.

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Comparison of Bone Morphogenetic Protein-2 Secretion Capacity of Myoma, Myometrium and Endometrium

Myom, Myometriyum ve Endometriyum Dokularının Bone Morfogenetik Proteini -2 Salgılama Kapasitesinin Karşılaştırılması

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ABSTRACT

Objective: Bone morphogenetic protein-2 (BMP-2) is a member of the transforming growth factor β3 (TGF-β3) family and plays a crucial role in decidualization and implantation. Myomas can adversely affect endometrial receptivity and embryo implantation. Recent studies have highlighted the importance of understanding the molecular mechanisms underlying endometrial receptivity. The objective of this study is to determine the BMP-2 secretion capacity of intramural, subserous, and submucous myomas, as well as their effects on BMP-2 levels in endometrial tissue.

Material and Method: Ninety-seven women who underwent hysterectomy or myomectomy because of symptomatic myomas were divided into three groups as submucous (SMM, n=26), intramural (IMM, n=34), and subserous (SSM, n=37). Myoma, myometrium and endometrial tissue samples were isolated and homogenized. BMP-2 concentrations of myoma, myometrium and endometrium tissue samples were evaluated with ELISA kits.

Results: BMP-2 levels showed no significant difference between myoma samples of SMM, IMM, SSM (p>0,05). Within the groups, endometrium of SMM have the lowest BMP-2 levels (2417±720 pg/ml, p<0.05). BMP-2 levels in endometrium of SSM and IMM groups were higher than myoma and myometrium of SSM and IMM groups. SMM group did not show any difference in BMP-2 levels in endometrium, myometrium and myoma.

Conclusion: Subserous, submucous and intramural myomas show different effect on BMP-2 expression in endometrium, myometrium and myoma. SSM and IMM have no impact on BMP-2 expression of endometrium. But SMM alter release of BMP-2 in endometrium. Decreased BMP-2 levels may be the responsible mechanism for impaired implantation and decreased pregnancy rates in this group of patients. Further investigations may lead to the development of novel therapeutics aimed at restoring BMP-2 levels.

Keywords: *Leiomyoma, BMP-2 protein, Infertility*

ÖZET

Giriş: Bone morfogenetik protein-2 (BMP-2), transforming growth faktörü β3 (TGF-β3) ailesinin bir üyesi olup, desidualizasyon ve implantasyonda kritik bir rol oynar. Miyomlar, endometrial reseptivite ve embriyo implantasyonunu olumsuz etkileyebilir. Son çalışmalar, endometrial reseptivitenin temelinde yatan moleküler mekanizmaların anlaşılmasının önemini vurgulamıştır. Bu çalışmanın amacı, intramural, subseröz, submuköz miyomların BMP-2 salgı kapasitesini ve endometrial dokuda BMP-2 seviyelerine olan etkilerini belirlemektir.

Materyal ve Metot: Semptomatik miyomlar nedeniyle histerektomi veya miyomektomi geçiren 97 kadın, submuköz (SMM, n=26), intramural (IMM, n=34) ve subseröz (SSM, n=37) olmak üzere üç gruba ayrıldı. Miyom, miyometrium ve endometrial doku örnekleri izole edilip homojenize edildi. Miyom, miyometrium ve endometrium doku örneklerinin BMP-2 konsantrasyonları ELISA kitleri kullanılarak değerlendirildi.

Bulgular: BMP-2 seviyeleri, SMM, IMM, ve SSM gruplarının miyom örnekleri arasında anlamlı bir farklılık göstermedi (p>0,05). Ancak, bu gruplar içinde, SMM grubunun endometriumunda en düşük BMP-2 seviyelerini saptandı (2417±720 pg/ml, p<0.05). SSM ve IMM gruplarının endometriumundaki BMP-2 seviyeleri, aynı gruplardaki miyom ve miyometrium örneklerinden daha yüksekti. SMM grubu, endometrium, miyometrium ve miyom dokuları arasında BMP-2 seviyelerinde farklılık göstermedi

Sonuç: Subseröz, submüköz ve intramural miyomlar endometriyum, miyometrium ve miyomdaki BMP-2 ekspresyonu üzerinde farklı etkiler gösterir. Çalışmamızda SSM ve IMM'ların endometriyumun BMP-2 ekspresyonu üzerine etkisi gösterilememiştir. SMM'lar ise endometriumda BMP-2 salınımını değiştirmiştir. Azalmış BMP-2 seviyeleri, bu hasta grubunda daha sık karşımıza çıkan implantasyonun bozulması ve azalmış gebelik oranlarından sorumlu mekanizma olabilir. BMP-2 seviyelerinin artırılmasını sağlayan tedaviler, gelecek çalışmalar için araştırma konusu olabilir.

Anahtar kelimeler: *Leiomiyom, BMP-2 protein, İnfertilite*

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INTRODUCTION

The role of uterine myomas in infertility has been hypothesized for many years. Several attempts have been made to demonstrate the relationship between these two topics seen common in reproductive-age women.

The incidence of myomas in unexplained infertility is approximately 1-2,4% and myomas are present in 10% of patients with infertility (Donnez and Jadoul, 2002). Studies evaluating the effects of myomas on infertility suggest that intramural myomas are related to decreased pregnancy rates while subserous myomas do not affect infertility (Bajekal and Li, 2000). Contrary to these, submucous myomas are found to be linked with infertility. And in these cases, myomectomy may increase pregnancy rates (Pritts et al., 2009). Despite the controversial data in the literature, submucous or cavity distorting myomas have more impact on pregnancy and implantation rates (Klatsky et al., 2008).

Data from many studies suggest that myomas decrease pregnancy rates by several different mechanisms. Distorted endometrial cavity, chronic endometrial inflammation, changes in uterine contractility, endometrial hormonal milieu and vascularization can be predisposing factors (Donnez and Jadoul, 2002; Rogers et al., 2008).

In a systematic review, Don et al revealed that fibroid-associated infertility could be potentially caused by alterations in the BMP- pathway in the endometrium, possibly leading to disturbed angiogenesis and reducing the success of implantation (Don et al., 2023)

Excessive production of extracellular matrix components can convert fibroid-related mechanical signals into biologic signals that affect the endometrium. Increased ECM stimulates the synthesis of transforming growth factor b (TGF-b) by altering intrafibroid microRNA production (Dokuzeylul Gungor et al., 2023)

Studies on underlying molecular mechanisms represent a growing field. Local growth factors secreted from myoma cells affect the myometrium and endometrium functions. TGF-β3 secreted from myomas impair expression of receptivity genes such as HomeoboxA10 (HOXA-10) and leukocyte inhibitory factor (LIF) (Arici and Sozen, 2000; Sinclair et al., 2011). Bone morphogenetic proteins (BMPs) are multifunctional growth factors that belong to the transforming growth factor β (TGF-β) superfamily. Studies report that BMP-2 expression in endometrium is necessary for successful homing, attachment and implantation of embryos (Li et al., 2007). TGF-β3 secreted from myomas inhibit endometrial BMP-2 activity by decreasing expression of BMP-2 receptors which results in decreased fertility rates.

In this study, we aimed to show BMP-2 secretion capacity of intramural, submucous and subserous myoma tissues and compare them with the BMP-2 levels of myometrium and endometrium.

MATERIAL and METHOD

Patient selection

We collected samples of myomas from 97 patients who were admitted to our hospital with symptoms such as pelvic pain, abnormal menstrual bleeding. These patients had undergone abdominal myomectomy or hysterectomy for these surgical indications and findings including endometrial hyperplasia, and endometrial polyp. We excluded patients who were using hormonal drugs or had evidence of other uterine, endometrial, or ovarian pathologies from the study groups.

Patients divided into 3 groups as submucous (SMM n=26), intramural (IMM n=34), and subserous myoma (SSM n=37) groups. Myoma, myometrium and endometrium tissue samples dissected from surgical specimens separately. Each surgical specimen was washed three times with sterile saline to remove blood, then transferred to RNAlater solution and stored at -80°C for future analysis.

Ethical approval

Ethical approval was issued by Istanbul Medipol University Ethical Committee with the registration number of 10840098-604.01-E.11889 in 2017. The procedures were in accordance with the ethical standards of the responsible local or national committee on human experimentation and with the Helsinki Declaration. Prior to specimen collection, all patients provided written informed consent.

Test principle of BMP 2

Myoma, endometrium and myometrium tissues minced to small pieces and rinsed in ice-cold Phosphate Buffered Saline (PBS) (1% mannitol, pH:7,4) to remove excess blood thoroughly. Tissue pieces weighed and then homogenized in PBS (tissue weight (g) / PBS volume (mL) = 1:9) with QIAGEN TissueLyser homogenizer. To further break the cells, samples sonicated with an ultrasonic cell disrupter or subject it to freeze-thaw cycles. The homogenates centrifuged for 5 min, at 5000 xg to get the supernatant. BMP-2 levels were measured in tissue samples by commercially available ELISA kits (E-lab science, E-EL-H0011, China) according to the manufacturer's specifications.

Statistical Analysis

The Statistical Package for Social Sciences, version 24.0 (SPSS Inc., Chicago, IL, USA) used for statistical analysis. BMP-2 and other individual group parameters assessed with one-sample Kolmogorov–Smirnov Z test and found abnormally distributed except age. Hence, statistical comparisons between groups performed by nonparametric Mann-Whitney

U test. ANOVA test is used for age. Kruskar wallis test used to compare three groups according to locations of myomas. Data presented as mean ± standard deviation (SD). For all comparisons, $p<0.05$ defined statistical significance.

RESULTS

A total of 97 patients included in the study. The study groups are divided into 3 groups according to localizations of myomas in the myometrium (submucosal myomas (SMM) n=26, intramural myomas (IMM) n=34 and subserous myomas (SSM) n=37). The mean age of patients was 44.09 ± 7.71 and did not show a significant difference between groups ($p>0.05$).

The results, as shown in Table 1, indicate that in SSM group BMP-2 levels were lowest in myoma (2524.84 ± 853.34 pg/ml). Endometrium showed higher BMP-2 levels than myoma and myometrium. There was a significant difference between endometrium and myoma samples ($p=0.020$).

Table 1. BMP-2 concentrations of myoma, endometrium and myometrium in subserous myoma group and comparisons between groups

	Subserous myomas	BMP-2 concentrations (pg/ml)
Group I	Myoma	2524.84± 853.34
Group II	Endometrium	3258.35± 458.19
Group III	Myometrium	3068.74± 400.44
	I vs II	0.020*
	I vs III	0.123
	II vs III	0.309

Mean ± SD, *p<0.05, BMP-2: Bone morphogenetic protein 2 (pg/ml)

Data from table 2 presents lower BMP-2 concentrations in intramural myoma samples compatible with subserous myoma group (2558.87±989.27 pg/ml). BMP-2 levels showed a significant difference between endometrium and myoma ($p=0.039$). As table 3 shows, endometrium and myometrium tissues did not show a significant difference in submucous myoma group.

Table 2. BMP-2 concentrations of myoma, endometrium and myometrium of IMM group and comparisons in between groups

	Intramural myomas	BMP-2 concentrations (pg/ml)
Group I	Myoma	2558.87 ± 989.27
Group II	Endometrium	3366.14 ± 345.35
Group III	Myometrium	3244.32 ± 325.47
	I vs II	0.039*
	I vs III	0.082
	II vs III	0.375

Mean ± SD, *p<0.05 BMP-2: Bone morphogenetic protein 2 (pg/ml).

Table 3. BMP-2 concentrations of myoma, endometrium and myometrium of SMM group and comparisons between groups.

	Submucous myomas	BMP-2 concentrations (pg/ml)
Group I	Myoma	2527.57 ± 990.13
Group II	Endometrium	2417.16 ± 719.89
Group III	Myometrium	2400.84 ± 803.06
	I vs II	0.655
	I vs III	0.565
	II vs III	0.749

Mean ± SD, BMP-2: Bone morphogenetic protein 2 (pg/ml)

Closer inspection of the table 4 presents that within the groups endometrial tissue BMP-2 concentrations showed a significant difference and SMM endometrium tissues have the lowest BMP-2 levels (2417±720 pg/ml, $p<0.05$). (Figure I).

Table 4. Comparisons of BMP-2 concentrations in myoma, endometrium and myometrium according to locations of myomas

BMP-2 (pg/ml)	IMM (n=34)	SSM (n=37)	SMM (n=26)	P value
Myoma	2524±853	2559±989	2528±990	0,892
Endometrium	3258±458	3366±345	2417±720	0,023*
Myometrium	3069±400	3244±325	2400±803	0,059

Mean ± SD, p<0.05, SS: Subserous myoma, SMM: Submucous myoma, IMM: Intramural Myoma, BMP-2: Bone morphogenetic protein 2 (pg/ml)

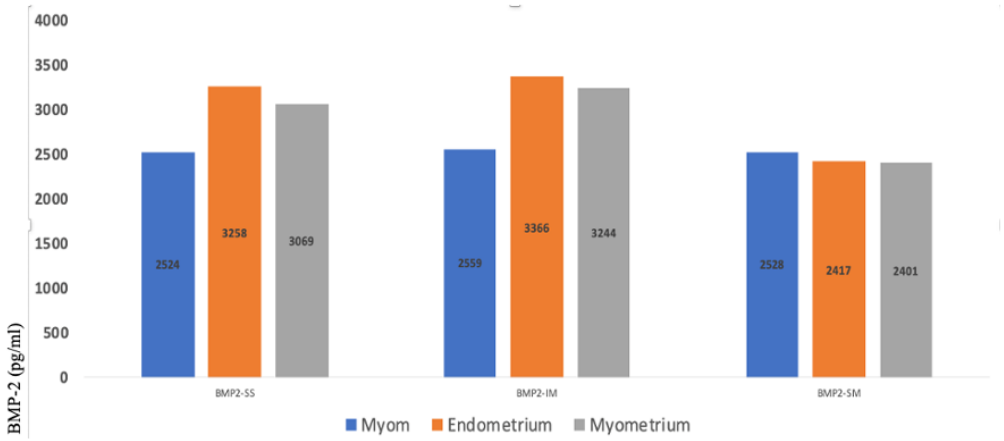

Figure 1. Comparisons of BMP-2 levels in myoma, endometrium and myometrium tissues according to the localization of myomas. BMP-2: Bone morphogenetic protein 2 SSM: Subserous myoma SMM: Submucous myoma, IMM: Intramural myoma

DISCUSSION

Uterine myomas are indolent benign tumors of women's reproductive system. Symptoms are usually associated with their size and location. It's well-known that submucous myomas can cause menorrhagia, abortion, pelvic pain even in small dimensions while subserous myomas are clinically asymptomatic. In this study, we aimed to show the difference among BMP-2 secretion levels of endometrium, myometrium and myoma tissues according to anatomic locations of myomas.

In our study, we showed that BMP-2 concentrations of myoma tissues in SSM-IMM groups are less than myometrium and endometrium of same patients. In SMM group, we showed no difference among myometrium, myoma and endometrium. Closer inspection of the results showed myomas secrete less BMP-2 and SSMs- IMMs do not affect BMP-2 concentrations of endometrium. In SMM group, BMP-2 concentrations showed no difference in endometrium, myometrium and myoma. With these results we concluded that submucous myomas, despite the small sample size, may influence BMP-2 concentrations of endometrium.

The literature on molecular effects of myomas on endometrium and endometrial receptivity have highlighted several mechanisms. Local growth factors secreted from myoma cells affect the myometrium and endometrium functions. Myomas are monoclonal tumors that secrete excess TGF-β3, which known to regulate transcription factors on endometrium. TGF-β3 secretion of myomas causes BMP-2 receptor resistance. In the implantation window, HOXA 10-HOXA 11 play a crucial role and BMP-2 receptor resistance causes down regulation of these proteins (Arici and Sozen, 2000; Sinclair et al., 2011) Likewise TGF-β3 secreted from myoma cells impair implantation promoting activity of BMP-2 signaling in the endometrium. BMP-2 expression in the endometrium is necessary for successful homing, attachment and implantation of embryos and decidualization (Zhao et al., 2018). Li et al. showed induction of BMP-2 during decidualization in vitro endometrial stromal culture (Li et al., 2007)

Endometrial tissues of patients with myomas have less BMP-2 levels compared to control groups (Sinclair et al., 2011) Doherty et al. showed in their study that myoma conditioned endometrial stromal cells present less BMP-2 response and concluded that TGF-β3 blockade could be a targeted therapy for myoma related infertility (Doherty and Taylor, 2015)

Many studies in the literature have emphasized that uterine structural anomalies like myomas, polyps and septums affect endometrial receptivity (Munro, 2019) Submucosal myoma samples expressed less endometrial HOXA 10 and HOXA 11 messenger RNA (mRNA) compared to IMM (Rackow and Taylor, 2010) Excision of submucous myomas is associated with increased clinical pregnancy and live-birth rates (Casini et al., 2006) A systematic review showed that patients with non-cavity distorting IMM have 15% decreased pregnancy rate in in vitro fertilization (IVF) cycles (Sunkara et al., 2010) A recent study by Unlu et al. reported that myomectomy of not cavity distorting intramural myomas improve endometrial receptivity by enhancing expression of homeobox genes (Unlu et al., 2016) On the other hand, a systematic review showed no difference in clinical pregnancy rate, live birth rate or miscarriage rate in patients with IMM and myomectomy of these tumors did not improve pregnancy rates (Metwally et al., 2011) In a review by Munro it was claimed that intramural myomas affect by paracrine ways and therefore the interspace between endometrium and myomas gain importance. Related with this it was concluded that myomas with less myometrial-endometrial distance most likely have negative effect on implantation (Munro, 2019)

Güngör et al. thought that fibroid derived- TGF-β3 diffusing into the endometrium and blocking BMP-2 receptors reduces LIF and HOXA levels. In their study, HOXA and LIF increased after performing myomectomy. They concluded that myomectomy reactivates endometrial BMP-2 receptors by eliminating TGF-β3-expressing cells, thus reinitiating HOXA and LIF production (Dokuzeylul Gungor et al., 2023).

This study has several potential limitations. The results from our small study need to be confirmed with larger studies. Endometrial receptivity and the implantation process are very complex and involve many factors working together. Because of this, it is hard to focus on the effect of just one factor and ignore the others. However, understanding how BMP2 affects implantation is an important step in exploring these processes.

Conclusion

Bone morphogenetic protein-2 (BMP-2) is part of the TGF-β3 family and plays a key role in implantation and the preparation of the endometrium. Myomas can negatively effect implantation. This study highlights that BMP-2 levels are lower in tissues with myomas, which may affect implantation and endometrial function. Understanding factors like BMP-2 could help create new treatments in the future, especially for patients with implantation failıres. Larger studies are needed, but knowing how BMP-2 and other pathways work can help in managing myoma cases and improving outcomes.

Conflict of Interest

The authors have no conflicts of interest relevant to this article.

Ethical approval

Ethical approval was issued by Istanbul Medipol University Ethical Committee with the registration number of 10840098-604.01-E.11889 in 2017.

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Investigation of the Relationship Between Reflux, Sleep Quality and Prenatal Attachment in Pregnancy

Gebelikte Reflü ile Uyku Kalitesi ve Prenatal Bağlanma Arasındaki İlişkinin İncelenmesi

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ABSTRACT

Objective: The aim of the study was to investigate the relationship between reflux in pregnancy, sleep quality and prenatal attachment.

Material and Method: The study was conducted with 180 pregnant women (case: 90, control: 90). Data were collected using the 'Reflux Symptom Index', 'Personal Information Form', 'Pittsburgh Sleep Quality Index' and 'Prenatal Attachment Inventory'. The research data were analyzed by chi- square, t- test and Pearson correlation analysis.

Results: In this study, the mean Pittsburgh Sleep Quality total index score of the case group was 11.13±3.25 and 7.02±2.54 in the control group, and the mean Prenatal Attachment Inventory score was 37.33±11.20 in the case group and 43.00±12.64 in the control group. In addition, it was observed that prenatal attachment levels of pregnant women in both groups decreased in parallel with the level of sleep quality.

Conclusion: In this study, it was concluded that sleep quality and prenatal attachment levels of pregnant women with reflux were lower than pregnant women without reflux and prenatal attachment levels decreased in parallel with sleep quality.

Keywords: *Prenatal attachment, Reflux, Sleep quality*

ÖZET

Giriş: Araştırmanın amacı; gebelikte reflü, uyku kalitesi ve prenatal bağlanma arasındaki ilişkinin incelenmesidir.

Materyal ve Metot: Araştırma 180 gebe kadın (vaka: 90, kontrol: 90) ile yürütülmüştür. Çalışma verileri, "Reflü Semptom İndeksi", "Kişisel Bilgi Formu", "Pittsburgh Uyku Kalitesi İndeksi" ve "Prenatal Bağlanma Envanteri" kullanılarak elde edilmiştir. Araştırma verileri ki-kare, t-testi ve Pearson korelasyon analizi değerlendirilmiştir.

Bulgular: Çalışmada istatistiksel olarak anlamlı şekilde olgu grubunun Pittsburgh Uyku Kalitesi toplam indeks puan ortalaması 11.13±3,25, kontrol grubunun 7.02±2.54; Prenatal Bağlanma Envanteri puan ortalaması vaka grubunda 37.33±11.20, kontrol grubunda 43.00±12.64 olarak saptanmıştır. Ayrıca araştırmada her iki grupta yer alan gebelerin prenatal bağlanma düzeylerinin uyku kalitesi düzeyine paralel olarak azaldığı görülmüştür.

Sonuç: Araştırmada reflüsü olan gebelerin uyku kalitesi ve prenatal bağlanma düzeylerinin reflüsü olmayan gebelere göre daha düşük olduğu ve prenatal bağlanma düzeylerinin uyku kalitesine paralel olarak azaldığı görülmüştür.

Anahtar kelimeler: *Prenatal bağlanma, Reflü, Uyku kalitesi*

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INTRODUCTION

Pregnancy, a time of physiological and psychological changes, is generally a period of special and positive emotions for women. However, it can also be a time of various challenges, including gastroesophageal reflux disease (GERD). GERD is a prevalent condition with significant health implications, affecting the quality of life of individuals and contributing to substantial healthcare costs worldwide (Heidelbaugh, 2018). While the exact prevalence varies, GERD is reported to affect 30-50% of pregnant women (Herregods et al., 2015; Heidelbaugh, 2018). In Turkey, epidemiological studies have shown a prevalence of GERD ranging from 19% to 25% in the general population (Sezer Yeşil and Öztürk, 2016; Bor, 2017). The pathophysiology of GERD during pregnancy is complex, with decreased lower esophageal sphincter pressure due to hormonal changes being a primary contributing factor (Yalaki and Kara, 2014; Turan et al., 2016). Reflux in pregnancy not only causes physical discomfort but also significantly impacts sleep quality (Nodine and Matthews, 2013; Mindell et al., 2015; Hu et al., 2024). Furthermore, emerging evidence suggests a potential link between reflux and impaired prenatal attachment. While the exact mechanisms are still under investigation, sleep disturbances caused by reflux can contribute to maternal anxiety and depression, which in turn can negatively impact the development of a secure mother-infant bond (Ghanbari-Homaie et al., 2022). Given the potential impact of reflux on maternal well-being and fetal development, it is crucial to investigate the interplay between reflux, sleep quality, and prenatal attachment in pregnant women. However, no study could be found in the literature review that examined the relationship between reflux during pregnancy and sleep quality and prenatal attachment. Therefore, this study was conducted to investigate the association between reflux during pregnancy and sleep quality and prenatal attachment level. This study aimed to examine the association between these factors and contribute to a better understanding of the challenges faced by pregnant women with reflux.

MATERIAL and METHOD

The study protocol was approved by the Aydın Adnan Menderes University, Faculty of Health Sciences, Non-Invasive Clinical Research Ethics Committee (No.: 2020/035). Subsequently, written permission was obtained from Tunceli Provincial Health Directorate to conduct the study in Tunceli State Hospital. This cross- sectional and case-control analytical study was conducted between September 24, 2020, and June 24, 2021, in the Obstetrics and Gynecology Clinic of Tunceli State Hospital affiliated with Tunceli Province. With the convenience sampling method, 180 pregnant women were included in the study, 90 in the case group and 90 in the control group. The sample size of the study was calculated as 156 pregnant women using the G-Power programme by using the study data of Yanıkkerem and Saruhan (2012). Pregnant women aged 18-37 years who can read and understand Turkish have a single fetus, are in the third trimester of pregnancy (between 28-40 weeks), and volunteered to participate in the study were included in study. In contrast, those who belong to the high-risk group of pregnancy and have any pregnancy complications and those with systemic and neurological diseases were excluded from the study. Research data were collected using Personal Information Form, Reflux Symptom Index, Pittsburgh Sleep Quality Index, and Prenatal Attachment Inventory.

The Personal Information Form was prepared by researchers based on the literature (Çoban and Yanıkkerem, 2010; Yeşilkaya, 2018). This form includes 12 questions that question the identifying characteristics of pregnant women.

Reflux Symptom Index (RSI) was developed by Belafsky et al. in 2002 and is a nine-title index designed to detect the presence of laryngopharyngeal reflux (Belafsky et al., 2002). An index score of ten or more indicates the presence of reflux. A score of 0 is considered unproblematic, and a score of 5 is regarded as a severe problem. The RSI has been used in studies to determine the presence of reflux. It has been shown to be reliable and valid (Ezerarslan et al., 012; Günel et al., 2012; Karaaltın et al., 2016; Verim et al., 2016). In this study, pregnant women with a score of 10 and above in the Reflux Severity Index were included in the case group, and pregnant women with a score below 10 were included in the control group.

Pittsburgh Sleep Quality Index (PSQI) was developed in 1989 by Buysse et al., the PSQI is a self- report test that provides information about sleep disturbances, sleep efficiency, type of sleep disturbances, and severity of sleep disturbances experienced in the past month. Its Turkish validity and reliability were performed by Ağargün et al. (1996). The Cronbach alpha value of the scale was 0.804. PSQI consists of 24 questions. Scores of 5 points or more on the scale are considered low sleep quality (Çoban and Yanıkkerem, 2010). In this study, the Cronbach alpha value was determined as 0.789.

Prenatal Attachment Inventory (PAI) was developed in 1993 by Mary Muller. It was adapted by Yılmaz and

Beji in 2009. This scale was developed to explain the thoughts, feelings, and situations that pregnant women experience and determine the degree of attachment to the baby during the prenatal period. A minimum of 21 points can be scored on this scale, and the maximum score is 84. The higher the score on the scale, the higher the degree of prenatal attachment. Yılmaz and Beji found that the Cronbach's alpha reliability coefficient of the scale is 0.84 (Yılmaz and Beji, 2013). In this study, Cronbach's alpha value was 0.78.

Statistical Analysis

Chi-square or t-tests were performed in independent groups to compare the personal and obstetric characteristics of the pregnant women in the case and control groups. An Independent groups t-test was used to compare the means of PSQI and PAI of the case and control groups, and Pearson's correlation analysis was used to examine the relationship between the means of PSQI and PAI.

RESULTS

It was found that the pregnant women in both groups who participated in the study had statistically similar university and post-university education levels, most of them were not employed, most of them had the same income, most of them lived in the city, most of them had a nuclear family structure, and their average age was close (Table 1). It was found that the pregnant women in the case and control groups who participated in the study had statistically similar first pregnancy i.e., the majority of them had no living child, a large proportion of them had no history of miscarriage or abortion, they mostly had planned pregnancy and the average week of pregnancy was close (Table 2). The study found that the pregnant women in the case group had higher total and subscale mean scores than the pregnant women in the control group, and this difference was statistically significant ((p<0,05) for the total and all subscales of the PSQI). In addition, the mean PAI scores of pregnant women in the case group (37.33±11.20) were statistically significantly lower than those of pregnant women in the control group (43.00±12.64) (p<0.05) (Table 3). In the study, a high negative correlation was found between the total and subscales of the PSQI and mean PAI scores in the case group (total scale score r: -0.791, p<0.001), while a moderate negative correlation was found in the control group (total scale score r: -0.498, p < 0.001) (Table 4).

Table 1. Distribution of personal characteristics of pregnant in the case and control group(n=180)

Characteristics	**Case Group (n = 90)n (%)**	**Control Group (n=90)n (%)**	**X²/p**
Educational status			
Primary Education High	16 (17.8)	15 (16.6)	2.220/0.
School University or	22 (24.4)	21 (23.4)	695
Higher	52 (57.8)	54 (60.0)	
Employment status			
Yes	17 (18.9)	18 (20.0)	0.224/0.
No	73 (81.1)	63 (80.0)	712
Income Status			
Income less than expenses	18 (20.0)	16 (17.8)	1.749/0.
Income equal to expenses	63 (70.0)	59 (65.5)	417
Income more than expenses	9 (10.0)	15 (16.7)	
Place of residence			
City	78 (86.6)	79 (87.8)	4.170/0.
Town	7 (7.8)	6 (6.6)	244
Village	5 (5.6)	5 (5.6)	
Family type			
Nuclear family	84 (93.3)	85 (94.4)	1.851/0.
Extended family	6 (6.7)	5 (5.6)	174
Characteristics	**Mean±SD (Min-Max)**	**Mean±SD (Min- Max)**	**t/p**
Age	27.11±4.38 (18-37)	28.28±4.62 (21-37)	0.600/0. 953

Table 2. Distribution of obstetric characteristics of pregnants in the case andcontrol group (n=180)

Characteristics	Case Group (n =90) n (%)	Control Group(n=90) n (%)	X^2/p
Total number of pregnancies			
One	44 (48.9)	49 (54.4)	0.933/
Two	25 (27.8)	24 (26.7)	0.8
Three	12 (13.3)	11 (12.2)	18
Four or more	9 (10.0)	6 (6.7)	
Number of living children			
One	32 (35.6)	29 (32.2)	0.031/
Two	8 (8.9)	8 (8.9)	0.5
None	50 (55.5)	53 (58.9)	41
Number of Miscarriages			
One	16 (18.8)	11 (12.2)	1.089/
No miscarriage	74 (82.2)	79 (87.8)	0.2
			97
Number of abortions			
One	10 (11.2)	9 (10.0)	0.225/
No abortion	79 (87.8)	81 (90.0)	0.6
			35
Planned pregnancy status			
Yes	83 (92.2)	83 (92.2)	0.009/
No	7 (7.8)	7 (7.8)	0.6
			90
Gestational week	34.33±3.75 (28-40)	34.29±3.76 (28-40)	0.079/
			0.9
			37

Table 3. Comparison of PSQI total and subscales and mean paı scores of pregnants inthe case and control groups

Scales	Case Group (n =90) Mean±SD (Min-Max)	Control Group (n=90) Mean±SD (Min- Max)	t/p
PSQI			
Subjective sleep quality	2.21±1.12 (0-3)	1.65±0.97 (0-3)	3.213/<0.001
Sleep latency	2.13±0.84 (0-3)	1.42±1.03 (0-3)	4.125/<0.001
Duration of sleep	1.92±0.54 (0-3)	1.13±0.74 (0-3)	4.325/<0.001
Habitualsleep efficiency	0.88±0.42 (0-3)	0.14±0.21 (0-3)	5.963/<0.001
Sleep disturbance	1.85±0.56 (0-3)	1.28±0.63 (0-3)	3.745/0.003
Use of sleeping pills	-	-	
Daytime dysfunction	2.52±0.91 (0-3)	1.94±0.74 (0-3)	3.854/0.002
Total PSQI	11.13±3.25 (0-3)	7.02±2.54 (0-3)	6.125/<0.001
PAI			
Total PAI	37.33±11.20	43.00±12.64	3.183/0.002

Table 4 The Relationship between the total and subscales of PSQI and PAI scores ofpregnant in the case and control group

PSQI	PAI	
	r	p
Case Group (n = 90)		
Sleep latency	-0.813	<0.001
Duration of sleep	-0.861	<0.001
Habitual sleep efficiency	-0.736	<0.001
Subjective sleep quality	-0.745	<0.001
Sleep disturbance	-0.882	<0.001
Use of sleeping pills	-	<0.001
Daytime dysfunction	-0.743	<0.001
Total PSQI	-0.791	<0.001
Control Group (n=90)		
Subjective sleep quality	-0,523	<0.001
Sleep latency	-0.485	<0.001
Duration of sleep	-0.423	<0.001
Habitual sleep efficiency	-0.599	<0.001
Sleep disturbance	-0.347	<0.001
Daytime dysfunction	-0.596	<0.001
Total PSQI	-0.498	<0.001

DISCUSSION

Our study demonstrated a significant association between gestational reflux, impaired sleep quality, and decreased prenatal attachment in pregnant women. These findings align with previous research that has linked reflux to various pregnancy complications (Çoban and Yanıkkerem, 2010; Amanak, 2020; Le et al., 2023). The observed association between reflux and poor sleep quality is consistent with findings from Hu et al. (2024) and aligns with the general understanding that gastrointestinal discomfort significantly disrupts sleep (Nodine and Matthews, 2013; Mindell et al., 2015). Our findings further emphasize the impact of reflux on sleep quality in pregnant women, with the mean PSQI score in the reflux group (11.13±3.25) being notably higher than that reported in other studies of pregnant women (Çoban and Yanıkkerem, 2010; Celik and Kose, 2017; Köybaşı and Oskay, 2017; Dikmen, 2020; Özhüner and Çelik, 2019). In our study, the discomfort and frequent awakenings caused by reflux likely contributed to poor sleep quality in the affected group. Dolua et al. (2020) also emphasized the significant impact of various factors, including physical discomfort, on sleep quality during pregnancy. These findings suggest that sleep disturbances are a significant concern for pregnant women experiencing reflux.

The finding of significantly lower prenatal attachment levels in the reflux group is novel and highlights a potentially crucial impact of reflux on maternal-fetal bonding. While the exact mechanisms remain to be fully elucidated, several pathways may be involved. Firstly, sleep disturbances caused by reflux can lead to increased fatigue, irritability, and anxiety, negatively impacting maternal mood and emotional regulation, which are crucial for establishing a secure attachment with the fetus (Ghanbari-Homaie et al., 2022). Secondly, the constant discomfort and emotional distress associated with reflux may divert maternal attention and energy away from focusing on the developing fetus. Ghanbari-Homaie et al. (2022) also highlighted the significant role of anxiety in influencing pregnancy outcomes, including maternal-fetal attachment. The present study indirectly supports this finding by demonstrating that reflux, which can be a significant source of anxiety during pregnancy, negatively impacting prenatal attachment. Therefore, it is important to conduct studies with different sample groups regarding the problem of reflux in pregnancy, which is predicted to negatively affect maternal and infant health. Our findings underscore the importance of early identification and management of reflux symptoms in pregnant women. Healthcare providers should routinely assess for reflux symptoms, address sleep disturbances, and provide emotional support to pregnant women experiencing reflux. Pregnant women should be questioned about their reflux symptoms and necessary precautions should be taken to raise awareness and manage symptoms, reduce discomfort and improve sleep quality of pregnant women. They should provide pregnant women with education on sleep hygiene, dietary modifications, and relaxation techniques. Healthcare professionals should encourage pregnant women to engage in regular exercise, maintain a healthy weight, and eat small, frequent meals. They should also address potential emotional issues like anxiety and depression that

may arise due to reflux and provide appropriate psychological support.

This study provides valuable insights into the multifaceted impact of gestational reflux on maternal well-being. By highlighting the significant associations between reflux, impaired sleep quality, and decreased prenatal attachment, our findings emphasize the need for comprehensive care for pregnant women with reflux. Early identification, effective management strategies, and continued research are essential to improve maternal health outcomes and promote optimal fetal development.

As a results improve overall health by identifying and treating chronic conditions that existed before pregnancy, to ensure complete mental and physical health during pregnancy, it should be ensured that potentially risky conditions are identified and treated early in the current pregnancy, and early treatment is provided, comprehensive and appropriate assessments of women for reflux, sleep quality, and prenatal attachment should be done, and they should be supported by professional health experts as needed.

Conflict of interest

The authors have no conflicts of interest in reporting.

Ethical approval

Approval for the research protocol was granted by the Non-Invasive Clinical Research Ethics Committee of Faculty Health Sciences, Aydın Adnan Menderes University (No.:2020/035). Subsequently, written permission was obtained from Tunceli Provincial Health Directorate to conduct the study at Tunceli State Hospital.

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Antioxidant Contents and Oxidative Stress Markers in Pediatric Familial Mediterranean Fever

Pediatrik Ailesel Akdeniz Ateşinde Antioksidan İçerikleri ve Oksidatif Stres Belirteci

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a non-genomic latent pathosis delineated by iterative attacks of fever with serositis. Variants of the FMF gene (MEFV) have been detected predominantly in patients from Mediterranean inhabitants. This study contemplates demonstrating the activity of antioxidants and oxidative stress in children diagnosed with FMF.
Material and Method: The study material comprised a range of 0-18 years of age of 35 individuals diagnosed with Familial Mediterranean Fever compared to 35 healthy participants. The study was conducted between 2016-2017. The samples were taken after the approval of Van Yüzüncü Yıl University, Medical Faculty of Research, education and Training Hospital, Department of Pediatric Health and Diseases Clinic and Research Laboratory Center. The studied enzymatic antioxidant activities such as in (GSH, GPx, and SOD) and the malondialdehyde (MDA) level, which represents the end-product of the lipid peroxidation process, the differences were revealed in the serum samples collected in distinction to patients diagnosed with FMF. The entirety of the analyses was conducted utilizing the SPSS statistics software package.
Results: In the estimation activity of GSH for the sera of patients, insignificant divergence was noticed at the time contrasted with comparator groups. The patient groups exhibited SOD activity that was revealed to be notably lower versus the healthy control group, showing statistical significance ($p<0.001$). Besides, no significant difference in serum GPx activity was discerned relative to the control group. The serum malondialdehyde (MDA) concentration was significantly elevated compared to the control groups. The distinction in the averages of GSH and GPx enzymes was found to be statistically insignificant, whereas the variance of MDA and SOD averages between the patient and control groups was found to be statistically significant ($p<0.05$). Hence, levels of MDA were elevated among the patients who endured Familial Mediterranean Fever disturbance. While, at the outset, the function of antioxidant enzymes such as SOD and GSH has shown a decline.
Conclusion: As a result of these grounds, alternative methods ought to be demonstrated in clinical applications for FMF patients, antioxidant enzymes might alter the underlying causes of the disease and its etiopathogenesis. Consequently, from our findings, we inferred that the reason for the progress and advancement of Familial Mediterranean Fever (FMF) disease might be the outcome of disruption and Inequity among the levels of antioxidants and oxidative stress (OS).

Keywords: *Familial Mediterranean Fever, GSH, GPx, SOD and MDA*

ÖZET

Giriş: Ailesel Akdeniz Ateşi (FMF), tekrarlayan ateş atakları ve serozit ile tanımlanan genetik olmayan bir patolojidir. FMF geninin (MEFV) varyantları ağırlıklı olarak Akdeniz bölgesinde yaşayan hastalarda tespit edilmiştir. Bu çalışma, FMF tanısı konan çocuklarda antioksidanların ve oksidatif stresin aktivitesini göstermeyi amaçlamaktadır.
Materyal ve Metot: Çalışma materyali, Ailesel Akdeniz Ateşi tanısı konan 0-18 yaş aralığındaki 35 hasta ve 35 sağlıklı katılımcıdan oluşuyordu. Çalışma 2016-2017 yılları arasında gerçekleştirilmiştir. Örnekler, Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği ve Araştırma Laboratuvarı Merkezi'nin onayından sonra alınmıştır. FMF tanısı konan hastalardan alınan serum örneklerinde enzimatik antioksidan aktiviteler (GSH, GPx ve SOD) ve lipid peroksidasyonunun son ürününü temsil eden malondialdehit (MDA) seviyesi ortaya konmuştur. Analizlerin tamamı SPSS istatistik yazılım paketi kullanılarak yapılmıştır.
Bulgular: Hastaların serumlarındaki tahmini GSH aktivitesinde, karşılaştırma gruplarıyla karşılaştırıldığında önemsiz bir sapma fark edildi. Hasta grupları, sağlıklı kontrol grubuna göre belirgin şekilde daha düşük ve istatistiksel anlamlılık gösteren SOD aktivitesi sergiledi ($p<0.001$). Ayrıca, serum GPx aktivitesinde kontrol grubuna göre anlamlı bir fark saptanmadı. Serum malondialdehit (MDA) konsantrasyonu kontrol gruplarına göre anlamlı olarak yükseldi. GSH ve GPx ortalamalarındaki farkın istatistiksel olarak önemsiz olduğu, ancak MDA ve SOD ortalamalarının hasta ve kontrol grupları arasındaki varyansının istatistiksel olarak anlamlı olduğu bulundu ($p<0.05$). Bu nedenle, Ailesel Akdeniz Ateşi bozukluğuna maruz kalan hastalarda MDA seviyeleri yükselmiştir. Başlangıçta, SOD ve GSH gibi antioksidan enzimlerin aktivitesi azalmıştır.
Sonuç: Bu gerekçelerin bir sonucu olarak, FMF hastaları için klinik uygulamalarda alternatif yöntemler gösterilmelidir. Antioksidan enzimler, hastalığın altında yatan nedenleri ve etiyopatogenezini değiştirebilir. Sonuç olarak, bulgularımızdan, Ailesel Akdeniz Ateşi (FMF) ilerlemesinin nedeninin, antioksidanlar ve oksidatif stres (OS) seviyeleri arasındaki bozulma ve dengesizliğin sonucu olabileceği sonucuna vardık.

Anahtar kelimeler: *Ailesel Akdeniz Ateşi, GSH, GPx, SOD ve MDA*

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INTRODUCTION

Free radicals are active compounds and proactive chemicals in the outermost orbital in the context of unshared electrons (Poljsak et al., 2013). Within the biological entity, the free radicals originate frequently from oxygen, nitrogen, and sulfur molecules. These particularly highly reactive molecules that are identified as free radicals are components within several groups of molecules that are known as Reactive Oxygen Species (ROS), Reactive Sulfur Species (RSS), and Reactive Nitrogen Species (RNS) (Lu et al., 2010). Reactive oxygen species have been implicated in the pathogenesis of numerous conditions. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) exhibit divergent characteristics, with detrimental and beneficial effects. (Valko, 2005).

ROS perceive both free radical and non-free radical oxygen-comprising molecules such as singlet oxygen (1/2 O_2), superoxide ($O_2{\cdot}-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH). Besides, there exist reactive species involving nitrogen, copper sulfur, and iron (Poljsak et al., 2013). The reactive nitrogen species (RNS) are produced from nitric oxide when it reacts with O_2•, resulting in the formation of $ONOO^-$•. In addition, RSS is effortlessly consolidated and thiols can generate reactive species by reacting with ROS (Lu et al., 2010). This resulted in attributing generation of high amounts of ROS with oxidative stress and mitigating the balance of redox (Poljsak et al., 2013). The dualistic role of ROS includes their function as secondary messengers in crucial intracellular signaling pathways, contributing to the development and propagation of cancerous traits in cancer cells. Additionally, ROS can trigger and induce cellular senescence and apoptosis, potentially acting as anti-tumor agents (Valko, 2005).

Both reactive oxygen & nitrogen species become visible as an outcome of the respiratory cycle and oxidative phosphorylation process that potentially affects biological macromolecules like cellular DNA, resulting in single-strand and double-strand breaks, and inducing ultimate triggers in mutagenic changes, cardiovascular diseases, cell aging, and cancerous tumor growth (Çekiç et al., 2013). ROS can directly induce oxidative damage to cells by harming nucleic acids, proteins, lipids, and cell membranes within tissues. Highly reactive free radicals are produced during cellular energy generation from food and oxygen. Additionally, exposure to factors such as microbial infections, intense exercise, and various pollutants or toxins like smoking emissions, Ionizing and UV rays, alcohol, biocides, and ozone can also trigger the formation of these conditions (Poljsak et al., 2013).

Each cell has complex antioxidant defense systems, consisting of both low- and high-molecular-weight components, to safeguard against reactive oxygen species (ROS). The defensive mechanisms encompass both endogenous (internally produced) and exogenous (acquired through diet) components (Çekiç et al., 2013). The accumulated replication of reactive oxygen species and reactive nitrogen species (ROS/RNS), whether originating from internal processes or external factors, is ascribed as oxidative stress (Valko, 2005).

In recent years, numerous studies have highlighted the association between oxidative stress, cellular senescence, and certain diseases. Conversely, in the modern world, our lifestyle tends to promote the overabundance of free radicals and reactive oxygen species (ROS) within our physiological systems and biological organs. This leads to an elevation in oxidative stress levels, coupled with a decrease in the antioxidant efficacy (Zamora et al., 2016). Sies first delineated oxidative imbalance as "an inconvenience in the prooxidant to antioxidant equilibrium in the beneficence of the former, affecting potential damage" (Poljsak et al., 2013). Eminently, oxidative stress aids in the progression of inflammatory diseases, cancer, cardiovascular conditions, Alzheimer's disease, cataracts, diabetes, autism, and the aging process (Lu et al., 2010).

The disease of Familial Mediterranean fever (FMF) stands as the most prevalent type of hereditary auto-inflammatory disorder, marked by recurring fever episodes accompanied by inflammation of serosal or synovial tissues, each episode lasting from 12 to 72 hours. Furthermore, untreated or inadequately managed patients suffering from Familial Mediterranean fever (FMF) face an elevated risk of developing secondary amyloidosis, which predominantly affects renal and vascular function. Colchicine, the current prevailing standard and conventional treatment for FMF patients, has been widely recognized as safe and effective. It proves successful in most patients, it lowers the occurrence of inflammatory episodes and diminishes the likelihood of amyloidosis development. Yet, presently there are no alternative treatments that are both effective and approved for Familial Mediterranean fever (FMF) patients who experience adverse reactions to colchicine. Additionally, reducing the dosage due to adverse effects may lead to reduced effectiveness. Furthermore, roughly 5-10% of FMF patients experience persistent inflammatory flare-ups, even when administered the maximum (1.5 to 2.0 mg/day) tolerable doses of colchicine. The majority of (FMF) Familial Mediterranean fever patients exhibit a genetic trait inherited in an autosomal recessive manner allied to mutations in the MEFV gene, responsible for encoding the protein called pyrin (Gül et al., 2015). Pyrin (also known as marenostrin), along with several proteins containing the pyrin domain, constitutes intracellular signaling modules associated with inflammation and is connected to autoinflammatory maladies. Alterations in the MEFV,

the gene responsible for encoding pyrin, result in Familial Mediterranean fever (FMF), marked by reiterative polyserositis in a recessive manner. These mutations are also linked, albeit to a minor degree, with diverse autoinflammatory afflictions. In the context of a Th1-associated autoimmune disease, possessing a mutation in MEFV may exacerbate the course of the disease, as evidenced by carriers observed among patients with non-Ashkenazi origin multiple sclerosis (Rabinovich, 2005).

MATERIAL and METHOD

For this study, samples of blood were gathered from a total of 70 individuals 35 healthy and 35 children diagnosed with Familial Mediterranean Fever (FMF), comprising both males and females. Each participant, whether healthy or diagnosed with FMF, contributed 4ml of blood obtained from the antecubital venous vein. This sample was evenly distributed, with 2 ml added to a biochemistry tube and the remaining 2 ml to an EDTA tube.

The entire study population included individuals ranging from 0 to 18 years of age, encompassing 35 patients diagnosed with Familial Mediterranean Fever and an additional 35 healthy individuals who served as the control group. Several biochemical parameters were evaluated utilizing serum samples. The ethical approval was attained from the ethical committee of Van Yüzüncü Yıl University, Educational Research and Training Hospital of Medical Faculty, specifically from the Department of Pediatric Health and Diseases Clinic and Research Center. Four milliliters of blood were smoothly withdrawn from both selected healthy and affected individuals as planned for the study. The gathered blood samples were subsequently centrifuged. at 5000 revolutions per minute for 10 minutes, after which the serum was isolated from the plasma. The isolated serums were employed to assess some antioxidant parameters like glutathione peroxidase (GPx), superoxide dismutase (SOD), reduced glutathione (GSH), and an assessment of the body's oxidative stress through malondialdehyde (MDA).

Analysis Methods

1. Assessment of superoxide dismutase (SOD) activity

Superoxide dismutase enzyme activation was dictated by the suggested technique employed by (Popov et al., 2003). The antioxidant SOD is a compound that disposes, scavenges, and suppresses the formation of free radicals and enhances the decomposition of hydrogen peroxide and molecular oxygen effectively mitigating the presence of superoxide radicals (O2-•) generated in the course of oxidative energy production. The indicated approach is entrenched in the optical density quantification obtained by utilizing xanthine and xanthine oxidase. This process involves the detection of superoxide radicals derived from the blue-colored formazan dye of the compound Nitro Blue Tetrazolium (N.B.T) This procedure includes identifying superoxide radicals produced from the blue formazan dye of Nitro Blue Tetrazolium (N.B.T) compound by measuring their absorbance at a wavelength of 560 nm. In the serum sample, the Superoxide dismutase that subsists hinders the interaction of formazan by eliminating O2-• (superoxide radicals) from the ambiance. During the trial circumstances and investigative parameters, one unit of SOD is defined as a 50% reduction in the rate of decline of the oxidant N.B.T.

% İnhibition = [(Blank OD – Sample OD) / Blank OD] x 100

2. Assessment of reduced glutathione (GSH) activity

In the erythrocyte destruction facilitated by EDTA, equipped with distilled water, the entire set of proteins that do not convey the sulfhydryl (SH) group is induced to settle with a precipitating solution. The measurement of reduced glutathione (GSH) was taken upon the reaction's conclusion, marking the attainment of the final product. That marked the formation and emergence of the yellow hue in the transparent fluid resulting from the sulfhydryl groups and DTNB (5',5'-(dithiobis 2-nitrobenzoic acid). The evaluation of the antioxidant reduced glutathione levels in EDTA blood was conducted by spectrophotometer at a wavelength of 412 nm, and the analysis was completed within 24 hours duration (Beutler et al., 1963).

Activity (mg / dl) = [(OD2 – OD1) / 13600 x E1 1.25] x 1000

OD1 = First absorbance prior to augmentation of DTNB.

OD2 = Second absorbance post augmentation of DTNB.

Both absorbances are read at a wavelength of 412 nm.

E1 = 1 as part of the analysis.

The molar absorptivity or extinction coefficient of the resulting yellow hue observed during the GSH and DTNB interaction is 13600.

3. Assessment of glutathione peroxidase (GPx) activity

The evaluation of Beutler's method approach was employed for determining the glutathione peroxidase enzyme activity. The underlying concept beyond this approach is rooted in the activity of the glutathione peroxidase that facilitates the oxidation of oxidized glutathione (glutathione: H2O2: oxidoreductase, EC 1.11.1.9) ensued arose as a result of the interaction and reaction of reduced glutathione and hydrogen peroxide wherein the enzyme Glutathione reductase (GSH-R) reduces oxidative glutathione (GSSG) to

GSH amidst NADPH and reduction in NADPH is observed and monitored at a wavelength of 340 nm.

Enzyme Activity (U/ml) = (ΔOD/t) * [(Vt) / 6.22*Vs)]

ΔOD = Absorbance changes consistent with time.

t = time

Vt= The overall volume of the reaction (ml).

Vs Sample volume (ml).

An optical density of 6.22 is observed for 1 mmol of NADPH in a light path of 1 cm.

4. Assessment of malondialdehyde level (MDA)

The interaction between fatty acids and free radicals leads to the production of malondialdehyde, representing lipid peroxidation's outcome. The assessment uses thiobarbituric acid that imparts a colored appearance (Gutteridge, 1995). 200 µl is required from the blood sample and should be transferred within one tube. The chemicals, Phosphate buffer (800 ml), BHT solution (25 ml), and %30 TCA (500 ml) were infused. The tubes were vortexed and kept in an ice bath for 2 hours. Next, they were centrifuged at a rate of 2000 rpm in 15 minutes. One milliliter of the supernatant was extracted and shifted to other tubes. Subsequently, 75 ml of EDTA plus 250 ml of TBA were appended. The tubes were vortexed and placed in a hot water bath within 15 minutes. Following that, permitted to equilibrate to 25 Celsius, and the absorbance was gauged utilizing a UV/Vis spectrophotometer at a wavelength of 532 nm.

C = F * 6.41 * A

C: Concentration.

F: Dilution factor.

A: Absorbance.

Statistical Analysis

The essential statistical information of the analyzed parameters was disclosed through the standard deviation. During pairwise comparisons between groups, the employed T-test achieves a normal deviation, whereas Mann-Whitney U statistics were implemented in cases where it was not achieved. A significance level of 5% was presumed, and all evaluations were conducted utilizing the SPSS statistical software package.

RESULTS

A substantial statistical relationship ($p<0.05$) was identified upon examining the enzyme SOD (superoxide dismutase) activity), as in (Table 1) between the levels of the control group (5.028 ± 2.198 U/L) and those of the patient group (1.876 ±1.400 U/L).

Upon the inspection of (GSH) reduced glutathione enzyme activity, the correlation amidst levels of the control group (0.018 ± 0.011 U/L) along with patient group levels (0.019 ± 0.009 U/L) were noted statistically ($p<0.001$) to lack a significant relationship.

When the activity of the glutathione peroxidase (GPx) enzyme was evaluated, the association among the levels of the control group (0.038 ± 0.040 U/L) and the patient group (0.047 ± 0.044 U/L) were revealed to exhibit a statistically ($p > 0.001$) non-significant relationship.

After determining the levels of MDA (malondialdehyde), a lipid peroxidation marker, a statistically significant correlation ($p<0.05$) was found among the control group levels (1.214 ± 0.214 U/L) and the patient group levels (1.521 ± 0.200 U/L).

Table 1. Evaluation as stated in the Reference group along with FMF patients.

Parameter	Control $\bar{X}$ ±SD (n= 35)	Patient $\bar{X}$ ±SD (n=35)
SOD (U/L)	5.028 ± 2.198 *	1.876 ± 1.400 *
GPx (U/L)	0.038 ± 0.040 ^	0.047 ± 0.044 ^
GSH (U/L)	0.018 ± 0.011 ^	0.019 ± 0.009 ^
MDA (µmol/L)	1.214 ± 0.214 *	1.521 ± 0.200 *

*: $p<0.05$ ^: $p>0.001$

The activity of (SOD, GPx, and GSH) of serums with (MDA) serum level of the study population.

Upon reviewing the yielded results during our assessment of the reduced glutathione (GSH) enzyme activity, as depicted in (Table 1), a comparison between the control group measurements (0.018 ± 0.011 U/L) as revealed in (Figure 1) besides the extent of the patient group (0.019 ± 0.009 U/L) revealed a statistically insignificant relationship ($p>0.001$).

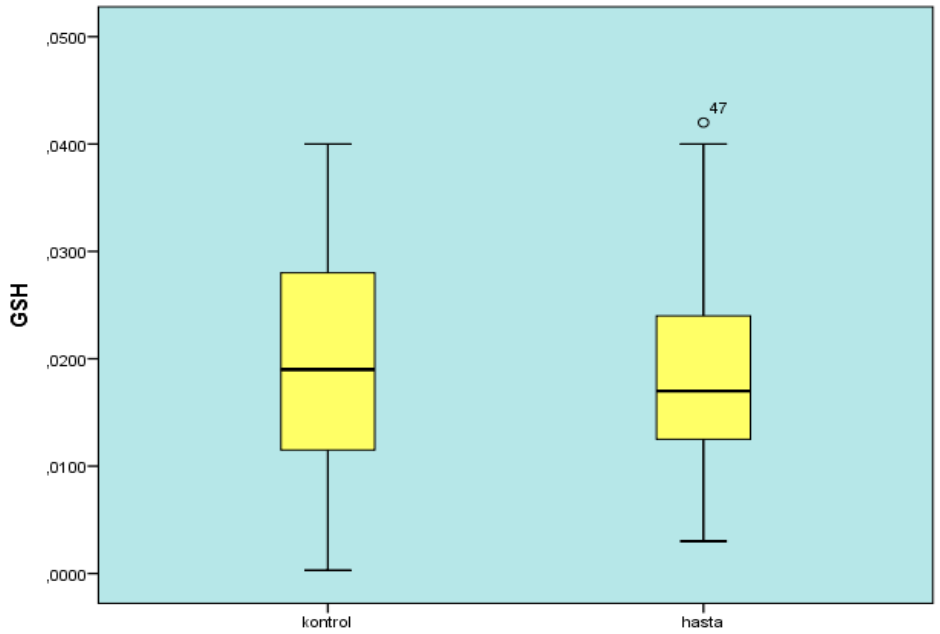

Figure 1. The activity level of GSH enzyme in both control participants and FMF patients

A significant statistical ($p<0.05$) relationship was observed in the evaluation of superoxide dismutase (SOD) enzyme activity, between the levels in the control group (5.028±2.198 U/L) and the patient group (1.876±1.400 U/L). Notably, the SOD enzyme activity as revealed in (Figure 2) in the patient group was comparatively below the SOD activity in the group that serves as the control.

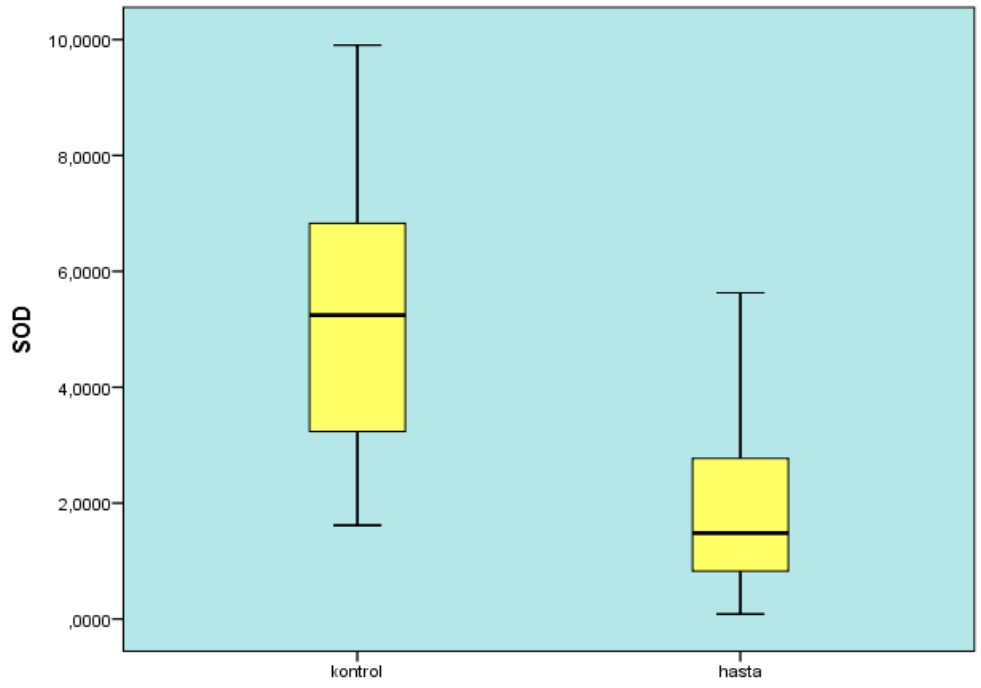

Figure 2. Activity of the SOD enzyme in both control participants and FMF patients

We assessed the enzyme activity of GPx (glutathione peroxidase) as shown in Table 1. Upon comparing the control group measures (0.038±0.040 U/L) besides the levels of patient groups (0.047 ± 0.044 U/L), a statistically insignificant relationship ($p>0.001$) was observed as revealed in (Figure 3).

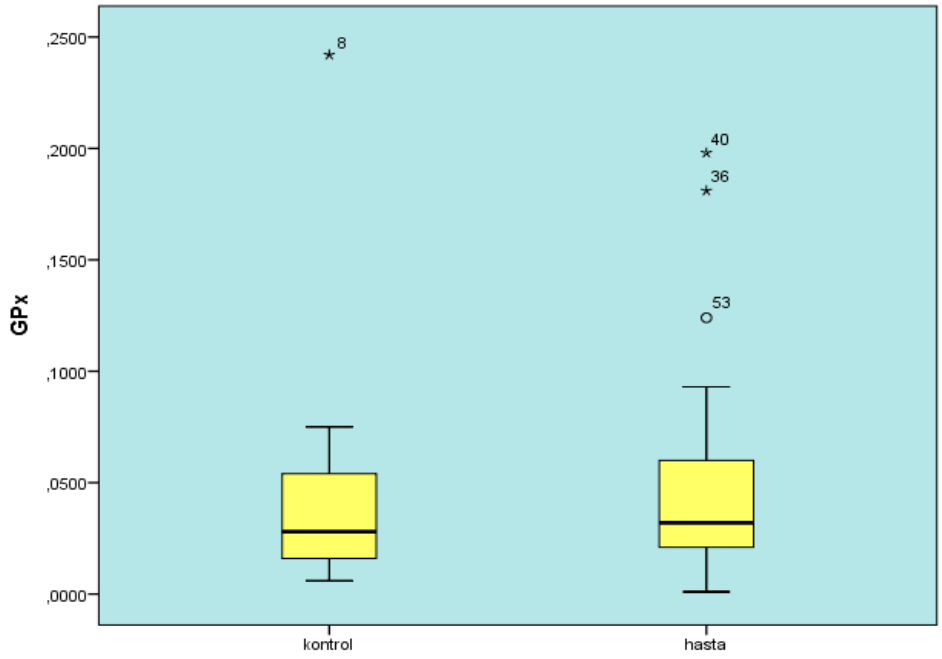

Figure 3. Activity level of GPx enzyme in both control participants and FMF patients

While investigating malondialdehyde (MDA) levels, a significant statistical ($p<0.05$) association was attained medially among the levels of the control group (1.214±0.214 U/L) and the patient group (1.521±0.200 U/L). As originated from (Table 1), the MDA level in the patient groups was relatively higher in comparison to the control groups, as evident revealed in (Figure 4).

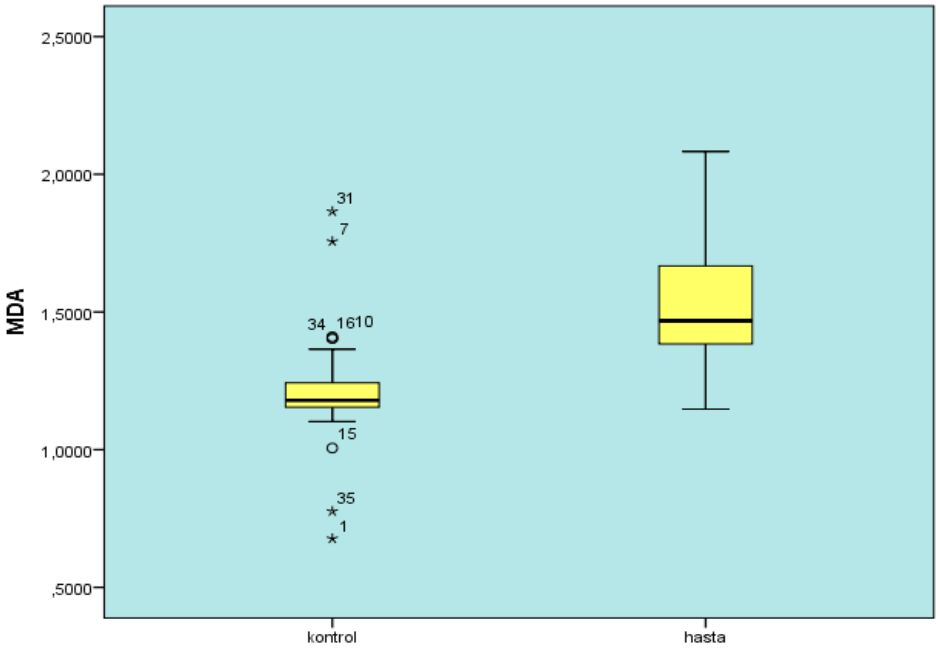

Figure 4. Levels of MDA in both control and FMF patients

DISCUSSION

This investigation analyzed and compared malondialdehyde levels in children, serving as an indicator of oxidative stress, among those diagnosed with familial Mediterranean fever disease, alongside alternative antioxidants like (GSH) reduced glutathione, (GPx) glutathione peroxidase, and (SOD) superoxide dismutase. Within biochemistry, sophisticated enzymology techniques play a pivotal and crucial role in curtailing and eradicating the detrimental effects of oxidants. This involves the utilization of various enzymes, both exogenous and endogenous antioxidants, characterized by their small molecular size. Ansari and Scheff established a strong association between diverse degenerative ailments and the extent of oxidative damage, encompassing markers like catalase, glutathione, SOD, thiobarbituric acid reactive compounds, protein carbonyl, acrolein, 4-hydroxynonenal & 3-nitrotyrosine (Ansari and Scheff, 2010). The current

study findings have not yet provided convincing evidence to ascertain the status of antioxidants in each organ when vulnerable to oxidative stress attacks. These attacks can potentially inflict harm and trigger participation and collaboration among genetic codes and protein-coding genes. Genetic alterations and molecular mechanisms specifically enable us to comprehend and highlight the free radical interactions. Additionally, they underscore the crucial role played by genomics, proteomics, and the progression of disease. Moreover, additional environmental factors, including oxygen tension and the transition metal concentrations, in terms of their oxidation-reduction status, will also play a crucial role in determining factors and resolution components (Rahal et al., 2014).

Glutathione peroxidases (GPxs) among eukaryotic organisms are recognized as the primary enzymatic defense in opposition to oxidative stress induced by hydroperoxides. Through harnessing the reducing capability offered by GSH, H2O2, and various organic hydroperoxides, like fatty acid hydroperoxides, undergo reduction to form the respective alcohols (Michiels et al., 1994). In certain studies, there has been a correlation between glucose intolerance and diabetes, where increased GPx activity was observed, while in others, a decrease in activity was noted. In a study, individuals suspected of having coronary disease and anticipated to have cardiovascular disorders exhibited low GPx activity (Morano et al., 2012). Nevertheless, their study found an insignificant association between (GPx) activity and cardiovascular disease. However, logically, the direction of the association aligned with previous studies. The cause of reduced (GPx) activity in cardiovascular disorders and its increase in the context of diabetes, which are often interconnected illnesses, remains ambiguous and uncertain. Studies conducted on animals demonstrate that the introduction of hydrogen peroxide initiates oxidative stress, resulting in the up-regulation of glutathione peroxidase (GPx). In cases of diabetes and persistent oxidative stress, one might anticipate increased activity of GPx due to this enzyme's upregulation. During myocardial infarction, characterized by acute oxidative stress, an excess production of free radicals might be noticed. Based on the obtained results, it is inferred that the activity of glutathione peroxidase (GPx) fluctuates with age and may be affected by particular diseases, as well as individual physical conditions (Espinoza et al., 2008).

FMF signifies an autoinflammatory disorder characterized by advancing inflammation levels. Inflammatory response functions predominantly in the advancement and atherosclerosis progression in certain rheumatic disorders. Throughout the inquiry, various measurements, including the MDA level, were employed to assess early indicators of atherosclerosis in FMF individuals. They found that MDA levels remained consistent among FMF patients in the interim of acute attacks and free periods. Among individuals with Familial Mediterranean Fever (FMF), irrespective of their oxidative stress status, the findings pointed towards an increased propensity for atherosclerosis over FMF alone. However, during this inquiry, we established a notable statistical correlation with a significance level ($p<0.05$) between both individuals when analyzing the MDA levels in healthy controls and FMF patients. Hence, the existence of additional inflammatory conditions among individuals suffering from FMF could modify their status of oxidative stress (Arıtürk et al., 2013). Our results align with recent literature. Consequently, elevated blood MDA levels can be regarded as a mitigating factor in studies assessing the risk of cancer.

Multiple studies have indicated that the acceleration of atherogenesis occurs significantly due to heightened autoimmune assaults and inflammation in inflammatory conditions characterized by elevated levels, as in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Recently, the correlation of atherogenesis with low-grade inflammatory conditions like ankylosing spondylitis as well as FMF has relatively surfaced, with ongoing studies progressively establishing this association. Yet, research exploring carotid atherosclerosis in individuals of FMF has identified a less aggressive atherogenesis progression than in high-grade inflammatory disorders. The researchers assessed various antioxidant marker levels for serum and whole blood during FMF-attack periods (AP) and FMF-attack-free periods (AFP). Additional researches are required to elucidate the lipoprotein (LDL and HDL) levels' impact on atherosclerosis in individuals experiencing FMF, considering the lipid-lowering effect of colchicine. Their findings exposed that FMF patients exhibit elevated oxidative stress levels during attack periods (Ediz et al., 2011). A study by Erden et al., demonstrated that colchicine that is employed in the regimen of knee osteoarthritis, elevates the capacity of the total antioxidants while reducing amounts of malondialdehyde. In vitro studies, particularly those conducted utilizing multidrug-resistant cell lines, have presented that colchicine elevates glutathione levels and GST activity (Erden et al., 2012). Hence, in many studies focusing on FMF, colchicine therapy seems to be associated with a less aggressive progression of atherogenesis. In this study, patient groups exhibited statistically significant elevations in LDL, ESR, and fibrinogen levels. No notable difference was observed between the groups referring to other biochemical parameters. The literature presents varying findings in FMF patients regarding levels of LDL and HDL (Gürbüz et al., 2016).

In a different study, scientists investigated the levels of oxidants and antioxidants in individuals with

familial Mediterranean fever (FMF) during both periods of attacks and attack-free intervals. They analyzed markers such as MDA, GSH, protein carbonyl (PC), and antioxidant vitamins (A, C, and E), as well as GPx and CAT activity in the serum and total blood of FMF patients. The concentrations of protein carbonyl (PC) and malondialdehyde (MDA) were notably higher ($P < 0.05$) in both the serum and total blood of FMF patients during attacks compared to attack-free periods. Additionally, the activities of GPx and CAT were notably reduced ($p<0.05$) during attacks in FMF patients compared to healthy individuals.

Moreover, no significant discrepancies were observed statistically within the levels of antioxidant vitamins between the healthy groups and patients. The ambiguous findings of the current study demonstrated increased oxidative stress levels during the attack period in patients suffering from FMF (Ediz et al., 2011).

An investigation addressing arthritis and rheumatoid arthritis (RA), both categorized under inflammatory disorders, highlighted those individuals with arthritis and rheumatoid arthritis experience oxidative stress, as indicated by significantly higher MDA levels ($p<0.01$) in comparison to healthy controls. Moreover, additional research revealed reduced amounts of both ascorbate (vitamin C) and α-tocopherol (an isoform of vitamin E) in arthritis and rheumatoid arthritis patients. Additionally, this implies a negative correlation between antioxidant levels and the inflammation present in the serum of these individuals (Sharma et al., 2014).

A widespread deficiency and considerably prevalent in children with FMF when compared to healthy individuals is vitamin D deficiency. Levels of 25(OH)D vitamin vary based on geographical location, skin complexion, sun exposure, and seasons. Certain investigators have suggested that low extents of Vitamin D might be an outcome of the inflammatory process, although this conclusion is not entirely definitive. However, this study provided clarification, indicating a negative correlation wherein Vitamin D levels decreased with increasing age. There were significantly fewer ($p<0.01$), levels of 25-hydroxy vitamin D observed among FMF patients and healthy controls with a higher prevalence among females (Onur et al., 2016).

The discrepancies in genetic mutations will impact the recognition given to FMF patients. In nearly the entire studies, the M694V mutation was recognized as the most prevalent. Additionally, serum amyloid A (SAA) levels upon entry were notably more elevated in individuals with homozygous M694V mutation as compared to those with heterozygous mutations or compound mutations. Additionally, it is indicated that fever, representing 97.3%, is the predominant symptom of FMF (Kilic et al., 2015).

Numerous findings have acknowledged the level of MDA as an indicator of the lipid peroxidation process. Patients with gastric cancer have shown elevated MDA levels in comparison to healthy individual groups. In a research investigation that examined levels of IL-18 in addition to MDA in patients suffering from renal cell carcinoma before surgery and following surgical intervention. The study found that the inflammatory mediator, IL-18, significantly increased after the surgery, alongside raised levels of MDA. Gender-based analysis revealed higher IL-18 concentrations and lower levels of MDA after surgery in the male group. Although IL-18 levels were elevated in the female group, there was no notable variation in MDA levels, while CAT activity showed an increase. Ultimately, the activity of the SOD enzyme showed an increase after surgery in both groups. This indicates that oxidative stress is not solely confined to cancerous cells besides extends to the entire organism (Didžiapetrienė et al., 2014).

The FMF prognosis is established after identifying the distinctive attributes and ruling out additional potential causes of periodic fever. Hence, diagnosing patients becomes challenging, particularly when the symptoms are less severe or present atypical manifestations of the infection. Within the clinical context of FMF, the existence of two mutations on separate alleles—whether homozygous or heterozygous may confirm the diagnosis. However, the diagnosis persists and remains inconclusive when a peerless mutation is detected. Per findings from a study aimed at identifying the fundamental genotypic distribution and diverse presentations clinically in FMF patients, as well as assessing the impact of colchicine therapy on these groups over one year. The disease's severity was evaluated according to the Severity Score of Tel Hashomer. Around one-third of FMF patients possess a single mutation on one allele. Conversely, in a single allele mutation situation, there might be an additional gene not yet fully identified responsible for the disease. The reasons leading to a lack of colchicine response may be elucidated by recognizing that colchicine should traverse different phases to modulate inflammation along its course, potentially influencing its efficacy at multiple points. Several factors, such as grapefruit juice, erythromycin, clarithromycin, simvastatin, lovastatin, cyclosporin, and others, can impact the effectiveness of colchicine by affecting its metabolism at the cytochrome 3A4 level.

Recent findings from a study involving 70 FMF patients primarily exhibited fever, abdominal pain, and arthritis, confirming these as the prevailing symptoms among homozygous, heterozygous, and undefined cases. The mutations E148Q, M680I, and V726A were identified as the most prevalent among the heterozygous group. The mean colchicine dosage necessary for the attack management was notably lower, and heterozygous group individuals displayed

a significantly more effective response to colchicine therapy than homozygous group individuals (Talaat et al., 2012). In the last years, a Turkish research group (Yalçınkaya-Özen) proposed novel parameters and guidelines used to diagnose FMF in children. The group determined that the pediatric criteria were more effective in identifying FMF symptoms in children during early years compared to Tel Hashomer and the Livneh criteria. The pediatric criteria yielded results more accurate and sensitive for diagnosing FMF among children (Demirkaya et al., 2013).

Regarding the metabolic impacts of colchicine, despite its ancient origins and historical use for gout treatment. Scholars note that it has been tested in numerous acute inflammatory contexts such as rheumatoid arthritis (RA) and during FMF acute episodes, despite its limited impact. Colchicine, an extracted portion derived from the colchicum autumnale plant, was recognized for treating acute gout in the sixth century and has been continually prescribed since then. Its impact might not be robust in small doses, yet its effectiveness relies on its interaction with different stages within the inflammatory response. Ultimately, the group of Tel Hashomer in Israel identified and endorsed colchicine as the preferred medication for managing and mitigating FMF following their investigation involving a cohort of 350 patients (Schwabe et al., 1977). Moreover, substantial colchicine usage at elevated doses resulted in notable adverse impacts. Exceeding a daily dosage of 1.8 mg of colchicine might induce fat malabsorption, D-xylose, and Vitamin B12. Furthermore, at higher doses, it may inhibit intestinal enzymes and potentially pose toxicity to the gastrointestinal mucosa, lungs, kidneys, bone marrow, and cardiovascular system. The safe recommended daily dosage, emphasized across various studies, typically ranges from 1 to 1.8 mg (Peters et al., 1983).

During a study involving 20 patients in the acute phase of FMF, a comparison was made against a group of 15 healthy controls. Indicators of the acute-phase reaction included fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte levels. Markers of lipid peroxidation were evaluated through measurements of conjugated diene, thiobarbituric acid reactive substances (TBARS), and lipid hydroperoxide concentrations. To assess the oxidation of DNA, the study evaluated 8-hydroxy-2-deoxyguanosine (8-OHdG). Additionally, the study analyzed thiol (T-SH) levels and carbonyl groups to indicate protein oxidative damage. Conversely, markers of antioxidant status such as (GSH) reduced glutathione level, (GPx) glutathione peroxidase, CuZn superoxide dismutase as well as the catalase activities were recognized and quantified. The levels of conjugated diene and carbonyl group were significantly surpassing ($p<0.001$) in individuals with FMF in comparison to healthy controls. Additionally, GPx activity revealed a significant decline ($p<0.01$) in FMF patients when compared to the group of individuals in good health. In the course of an attack, FMF patients exhibited substantially greater levels ($p < 0.001$) of ESR, CRP, leukocytes, and fibrinogen in comparison to those within the course of the attack-free period. FMF patients exhibited significantly reduced Cu-Zn SOD activity ($p < 0.05$) during the attack period. with higher T-SH levels ($p < 0.05$). Hence, the findings indicated an elevation in the acute phase response (APR) and elevated measurements of (OS) oxidative stress in FMF patients as related to healthy controls and individuals during the period of the attack (Guzel et al., 2012). Furthermore, this study highlights the discrepancy in SOD and Cu-Zn SOD behaviors. Contrary to previous findings where SOD levels were more elevated than controls, the assessments conducted during periods of the attack and attack-free, exhibited distinct outcomes. Therefore, more comprehensive studies will elucidate the conclusive outcomes. Oxidative stress levels escalate during the painful episodes of this disorder. The cause of this stress, whether it stems from FMF symptoms or other unidentified factors, isn't entirely clear. However, enhancing antioxidant defenses might help alleviate the symptoms. Furthermore, some available evidence suggests that boosting tissue antioxidant levels through dietary α-tocopherol supplementation can help prevent lipid peroxidation. Dietary supplementation with α-tocopherol has shown potential benefits in FMF treatment, hence prompting the need for further investigations (Karaguezyan et al., 1996).

There's an emerging body of evidence suggesting that genetic changes might heighten susceptibility to oxidative stress, and conversely, oxidative stress could potentially cause genetic alterations. The correlation between gene alterations and oxidative stress holds particular significance within various chronic conditions like neurodegenerative ailments, cancer, and cardiovascular diseases. The tumor suppressor gene p53 is a prime example of susceptibility to oxidative stress. It holds a critical role in controlling cell growth to inhibit cancer development, and it's notably impacted by oxidative stress. Exactly, high levels of oxidative stress can induce alterations or mutations in p53, potentially contributing to the onset of cancer.

Genetic alterations can indeed impact inherited immunity and the regulation of oxidative stress, contributing to various health conditions. Certainly, the partial penetration or varying expressivity of the R202Q mutation might impact the manifestation of the autoinflammatory disease across different ethnic populations (Milenković et al., 2016). Similar outcomes were observed when comparing patients of M694V homozygous in conjunction with another homozygous individual or the combination of the

remaining three mutations in a heterozygous state. Patients homozygous for M694V experienced an increased frequency of attacks within a month ($P<0.001$) and a notably higher ($p<0.015$) occurrence of arthritis (Brik et al., 1999). Research conducted in Iran reported and revealed by the FMF registration center that mutations of M694V-M694V were the most prevalent and frequently observed mutations among patients over ten years. Additionally, during the last ten years, the V726A-M694V mutation combination was frequently observed in those presenting with the disease. Younger patients predominantly exhibit the homozygous mutation M694V, presenting with primary symptoms like abdominal pain and joint involvement. This genotype shares similarities with those found in Arab and Armenian populations (Salehzadeh, 2015).

A recent study highlighted FMF as the primary cause of amyloidosis in Turkish patients. It was reported that the highest occurrence of FMF (1 in 123 individuals) was identified in the Tokat region of Turkey. Abdominal pain can vary in intensity, ranging from dull discomfort to severe, mimicking symptoms of an acute abdomen. Furthermore, it's often misdiagnosed as appendicitis, resulting in unnecessary appendectomies. Patients exhibiting the observable characteristics and identified mutations associated with Familial Mediterranean Fever (FMF) are categorized as phenotype I, while those in phenotype II develop amyloidosis without preceding distinct FMF attacks (Yilmaz and Ozer, 2010). Studies suggest that the triggers for recurrent disease attacks remain uncertain and could stem from physiological, emotional, or physical stress, menstrual cycles, dietary changes, and other ambiguous factors. In a recent study utilizing a case-crossover design, researchers identified an affirmative and significant association statistically between stressful incidences and the occurrences of attacks of FMF (Ktsoyan et al., 2013).

Research suggests that patients of FMF face an elevated susceptibility to cardiovascular disease in comparison to the broader community. The study focuses on assessing the significance of inflammation in FMF patients and individuals following standard intervention and comparing it to dialysis patients, who are presumed to be at higher risk of developing cardiovascular disorders. Additionally, they elucidated the link between the pathophysiological impacts of acute phase proteins and inflammation, a crucial aspect for complications arising from Familial Mediterranean Fever (FMF) ailment management (Akalin et al., 2015).

Given the potential for amyloidosis despite mild inflammation, several analyses have aimed to identify subclinical infection-signaling inflammation in FMF patients, seeking new indicators for this purpose.

At a level of inflammation individuals with Familial Mediterranean Fever (FMF) not exhibiting overt clinical symptoms increase onset complications such as heart disease, anemia, decreased bone mineral density, splenomegaly, and notably amyloidosis, which can pose life-threatening risks. Inflammation typically arises from the release of pro-inflammatory cytokines via macrophages and monocytes. α-TNF, IL-1, IL-6, and sIL-2r exhibit significant involvement during acute FMF episodes. Contrastingly, in interludes devoid of attacks, there is an elevation in the levels of IL-1b among individuals diagnosed with Familial Mediterranean Fever (FMF), correlating with levels of CRP. Moreover, IL-1b levels might serve as a significant indicator of subtle inflammation observed during periods devoid of attacks. within FMF patients. Among patients with Familial Mediterranean Fever (FMF) who are in attack-free phases, measurements of interleukins (IL-6, IL-8) and α-TNF were also detected. The study highlighted the neutrophil/lymphocyte ratio (NLR) as a dependable indicator of inflammation in FMF. The NLR exhibited a significant elevation statistically in individuals with chronic renal failure compared to individuals of good health. Additionally, the quantities were observed to increase concerning the severity of chronic renal failure. NLR serves as a useful indicator to identify inflammation undergoing hemodialysis or peritoneal dialysis in patients, those with cardiac issues particularly myocardial infarction, type 2 diabetes mellitus, and endometriosis, much like in the case of final-stage renal disease. This marker, derived from a complete blood count (CBC), offers a straightforward way to detect subclinical inflammation without incurring additional costs (Özer et al., 2015).

When conducting my literature review, I didn't encounter any studies identical to mine. Besides, a near investigation was found. The study encompassed individuals aged 20 to 40, aiming to delineate the oxidant and antioxidant statuses among FMF patients within courses of both attack period (AP) and attack-free periods (AFP) intervals. The MDA activity was significantly ($p <0.05$) elevated in both samples of serum and total blood obtained from the FMF individuals during the attack period in contrast to the other groups. CAT and GPx activities during the attack-free period, the levels in the FMF individuals revealed a decline ($p < 0.05$) in comparison to the healthy control group. Nevertheless, no significant variations were observed statistically in the amounts of antioxidant vitamins among the groups. So, it could be inferred that the influence and significance of antioxidant levels are greater in children than in adults (Ediz et al., 2011).

Conclusion

Consequently, patients with familial Mediterranean fever displayed elevated MDA levels. Initially, a decline was observed in the action of antioxidant enzymes, like superoxide dismutase (SOD) and reduced glutathione (GSH). Novel clinical approaches should be demonstrated for patients suffering from Familial Mediterranean Fever (FMF), due to these reasons and considering the potential impact of antioxidant enzymes on the disease's etiopathogenesis. Additionally, the clinical assessment of increased MDA levels, a byproduct of lipid peroxidation and indicative of oxidative stress, should prompt further studies for potential treatment approaches. We anticipate that this study will illuminate future research endeavors.

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Author Contribution Statement

The authors confirm their contribution to the paper as follows: study conception and design: Amani Tahsin YASIN, Halit DEMIR; data collection: Lokman ÜSTYOL, Şükran AKGEYİK, Rabia AKGEYİK; analysis and interpretation of results: Halit DEMIR, Canan DEMİR, Amani Tahsin YASIN; draft manuscript preparation: Amani Tahsin YASIN**.**

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Ethical approval: The study was approved by the Clinical Research Ethics Committee of Yüzüncü Yıl University Faculty of Medicine (18.12.2015-13). This study was conducted in strict accordance with the principles stated in the Declaration of Helsinki. Informed consent was obtained from the participants of this study.

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Metil Paratiyon Uygulanan Sıçanlarda *Nigella Sativa L.* Ekstraktının Karaciğer Koruyucu, Toplam Oksidan (TOS) ve Toplam Antioksidan (TAS) Kapasite Üzerine Etkisinin Araştırılması

Investigation of The Effect of Nigella Sativa L. Extract on The Liver Protective, Total Oxidant and Total Antioxidant Capacity in The Methyl Parathion Administered Rats

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ABSTRACT

Objective: This study was planned to evaluate the protective effect of Nigella sativa L. extract on acute and chronic toxicity of methyl parathion.

Material and Method: : In this study, 56 adult male Albino Wistar rats were used and randomly divided into 4 groups. In group 1, animals were given 1 mL distilled water and were considered as control group. In Group 2, 1/50 lethal dose of methyl parathion was given orally at 0.28 mg/kg/day for 28 days. In Group 3, 300 mg/kg/day Nigella sativa L. extract was given orally for 28 days. In group 4, 300 mg/kg/day Nigella sativa L. extract was administered orally 2 hours after 0.28 mg/kg/day methyl parathion was administered. Serum liver enzymes, total oxidant/antioxidant capacity, antioxidant vitamins (A, C, E), albumin, total cholesterol, triglyceride, total protein and liver histopathology were analysed.

Results: Serum aspartate aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP) and total cholesterol levels increased statistically in methyl parathion-treated group 2 compared to the other groups (especially group 4) and serum albumin and vitamin E levels decreased statistically ($p<0.05$). In addition, lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), VLDL cholesterol and total oxidant capacity levels increased, but this increase was not statistically significant ($p>0.05$). In group 2, serum total protein, total triglyceride, total antioxidant capacity, vitamin A and C levels decreased ($p>0.05$), this decrease was not statistically significant ($p>0.05$).

Conclusion: The protective effect of *Nigella sativa L.* extract on the liver was found to be statistically significant. Nigella sativa L. extract can be given as a food supplement for protective purposes against methyl parathion-like toxicities.

Keywords: *Methyl parathion, Nigella sativa, Total antioxidant/oxidant Capasity, Liver histopathology*

ÖZET

Giriş: Bu çalışma, metil paratiyonun akut ve kronik toksisitesi üzerine Nigella sativa L. ekstraktının koruyucu etkisinin değerlendirilmesi amacıyla planlandı.

Materyal ve Metot: Bu çalışmada 56 yetişkin erkek Albino Wistar sıçan kullanıldı ve rastgele 4 gruba ayrıldı. Grup 1'de hayvanlara 1 mL distile su verildi ve kontrol grubu olarak değerlendirildi. Grup 2'de hayvanlara metil paratiyonun 1/50 letal dozu 0,28 mg/kg/gün, 28 gün süreyle oral yolla verildi. Grup 3'te hayvanlara, 28 gün süreyle 300 mg/kg/gün Nigella sativa L. ekstraktı oral yolla verildi. Grup 4'te hayvanlara 0,28 mg/kg/gün metil paratiyon verilmesinden 2 saat sonra 300 mg/kg/gün Nigella sativa L. ekstraktı oral yolla verildi. Serum karaciğer enzimleri, toplam oksidan/antioksidan kapasite, antioksidan vitaminler (A, C, E), albumin, total kolesterol, trigliserit, total protein ve karaciğer histopatolojisi incelendi.

Bulgular: Metil paratiyon uygulanan grup 2'de serum aspartat aminotransferaz (AST), alanin amino transferaz (ALT), alkalin fosfataz (ALP) ve toplam kolesterol diğer gruplara göre (özellikle grup 4) istatistiksel olarak arttı aynı zamanda serum albumin ve vitamin E düzeyleri istatistiksel olarak azaldı ($p<0.05$). Ayrıca, laktat dehidrogenaz (LDH), gama glutamil transferaz (GGT), VLDL kolesterol ve toplam oksidan kapasite düzeyleri artış gösterdi, bu artış istatistiksel olarak anlamlı bulunmadı ($p>0.05$). Grup 2'de serum toplam protein, toplam trigliserit, toplam antioksidan kapasite, vitamin A ve C düzeyleri azaldı ($p>0.05$), bu azalma istatistiksel açıdan önemli bulunmadı ($p>0.05$).

Sonuç: *Nigella sativa L.* ekstraktının karaciğer üzerine koruyucu etkisi istatistiksel önemde tespit edildi. Nigella sativa L. ekstraktı metil paratiyon benzeri toksisitelere karşı koruyucu amaçlı gıda takviyesi olarak verilebilir.

Anahtar kelimeler: *Beslenme, beslenme alışkanlıkları, üniversite öğrencileri*

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GİRİŞ

Besinlerin üretimi, tüketimi ve depolanmaları esnasında, besin değerini düşüren ve besinleri yok eden, zararlı haşereleri, mikroorganizmaları ve diğer zararlıları ortadan kaldırmak amacıyla kullanılan kimyasal maddelerine pestisit denir. Pestisitlerin kullanılmasıyla tarımda büyük yararlar sağlanmaktadır. Pestisitlerin çevre kirliliği oluşturması nedeniyle toprakta ve suda uzun süre kalarak zehirli etkiler oluşturdukları bilinmektedir (Vural, 1996).

Metil paratiyon, organofosforlu bir pestisittir, düşük fiyat ve yüksek aktivitesi nedeniyle tarımsal üretimde yaygın olarak kullanılmaktadır (Govindasamy ve ark., 2017). Çiftliklerde ve tarım alanlarına yakın yaşayan bireylerin organofosforlu pestisitlere maruz kalma riskleri bulunmaktadır. Bu pestisitler su, hava, toprak ve gıdalar yoluyla insan vücuduna girebilir (Bian ve ark., 2010).

Organik fosforlu pestisitler grubunda yer alan en fazla kullanılan beş pestisitten biri olan metil paratiyonun moleküler formülü $C_{10}H_{14}NO_5PS$ olup, yüksek toksisiteye sahip ve moleküler ağırlığı 291,26 g/mol'dur. Zehirlenme vakalarında en önemli organ olan karaciğer, pestisitlere ve kimyasal maddelere karşı çok duyarlıdır. Bunun nedeni, vücuda alınan pestisitlerin ve bütün kimyasal maddelerin vücut içerisine alındıktan sonra biyotransformasyona uğradığı ilk organın karaciğer olmasıdır. İnsektisitlerin ve kimyasal maddelerin aktivasyonu ile aktif metabolitler hepatotoksik maddelere dönüşerek karaciğer bozukluklarının patolojisine ve etiyolojisine neden olurlar (Kalender ve ark., 2007).

Nigella sativa, Ranunculaceae familyasından olup önemli tıbbi ve aromatik bir bitkidir. Nigella cinsi ülkemizde 12 çeşidi ile temsil edilmektedir, bunlar içerisinde ülkemizde tarımı yapılan çeşidi *Nigella sativa L.* türüdür (Turan, 2014). *Nigella sativa L.* tohumlarının yapısında, uçucu yağlar, sabit yağlar, proteinler, tanenler, amino asitler, saponinler, alkoloidler, lifler, mineraller, karbonhidratlar, tiamin, pridoksin, niasin, askorbik asit ve folik asit bulunmaktadır. Sabit yağın yapısında doymamış yağ asitlerinden oleik asit, linoleik asit, Eikosenoik ve araşidonik asit bulunurken, doymuş yağ asitlerinden ise stearik asit, palmitik asit ve miristik asit bulunmaktadır. Uçucu yağın yapısında ise karvakrol, nigellon, p-cymene, ß-pinen ve d-limonen'in yanında farmakolojik olarak aktif temel bileşenlerden olan timol, timokinon, timohidrokinon ve ditimokinon yer alır (Randhawa ve Al Ghamdi, 2002).

Bu çalışmada; Metil paratiyonun sıçan karaciğeri üzerindeki toksisitesinin histopatolojik ve biyokimyasal olarak değerlendirilerek metil paratiyondan kaynaklı hepatotoksik hasara karşı *Nigella sativa L.* ekstraktının koruyucu etkisinin belirlenmesi amaçlandı.

MATERYAL ve METOT

Çalışmada, Van YYÜ Deney Hayvanları Araştırma ve Uygulama Merkezi'nden temin edilen elli altı (56) adet erkek Wistar-Albino sıçanlar (300–350g) kullanıldı. Deney hayvanları; özel kafeslerde tutuldu ve standart sıçan yemi ile beslendi. 12 saat ışık/karanlık periyodunda ve 18–22 ^oC'de muamele edildi. Her kafeste, 14 sıçan yer aldı, uygulama öncesi 15 gün boyunca deneme hayvanları karantinaya alındı. Çalışma, Van YYÜ Hayvan Deneyleri Yerel Etik Kurulu'nun 05.09.2014 tarih ve 2014/10 sayılı izin ile gerçekleştirildi.

Deneme gruplarının oluşturulması

Gruplar, her grupta 14 sıçan yer alacak şekilde rastgele;

1.Grup; Kontrol grubu (K)

2.Grup; Metil paratiyon grubu (MP)

3.Grup; *Nigella sativa L.* ekstraktı grubu (NS)

4.Grup; Metil paratiyon+*Nigella sativa L.* ekstraktı grubu (MP+NS) oluşturuldu.

Deneme gruplarına metil paratiyon uygulanması

Karaciğer toksikasyonu oluşumu ve *Nigella sativa L.*' ekstraktının koruyucu etkisini tespit amacıyla, 2. grupta (metil paratiyon) ve 4. grupta (metil paratiyon+*Nigella sativa L.*) yer alan sıçanların her birine günlük 0,28 mg/kg (1/50 LD 50) dozunda metil paratiyon (%99 saflıkta) mısır özü yağı içinde çözdürülerek intragastrik gavaj yoluyla verildi (Kalender ve ark., 2007).

***Nigella sativa L.* ekstrakt hazırlanması ve deneme gruplarına uygulanması**

Nigella sativa L. tohumu, elektrikli değirmende toz haline getirildi, kullanıma kadar +4 ^oC'de saklandı. Soksalet ekstraksiyon düzeneği ile yeterli miktarda %96'lık etanolde ekstrakte edildi. Etanol 40-50 ^oC'de düşük basınç altında uçuruldu ve elde edilen ekstrakt +4 ^oC'de saklandı (Hadjzadeh ve ark., 2007). *Nigella sativa L.* ekstraktı %5 sodyum karboksimetil selüloz (Na-CMC) distile su içinde çözdürülerek homojen solüsyon haline getirildi. 3. grupta (*Nigella sativa L. grubu*) yer alan sıçanların her birine *Nigella sativa L.* ekstraktı intragastrik gavaj yoluyla verildi. 4. grupta (metil paratiyon+*Nigella sativa L. grubu*) yer alan sıçanların her birine, metil paratiyon uygulamasından iki saat sonra günlük 300 mg/kg/gün dozda intragastrik gavajla verildi (Hadjzadeh ve ark., 2007).

1. Grup (Kontrol grubu): Birinci gün distile su verildikten 24 saat sonra 7 adet sıçan uyutuldu ve geri kalan 7 adet sıçana 28 gün boyunca distile su intragastrik gavaj yoluyla verildi.

2. Grup (Metil paratiyon grubu): Birinci gün metil paratiyon intragastrik gavaj yoluyla verildi. 24 saat sonra 7 adet sıçan uyutuldu ve geri kalan 7 adet sıçana 28 gün boyunca metil paratiyon ağızdan günlük 0,28 mg/kg (1/50 LD_{50}) dozunda mısır özü yağı içinde çözdürüldü, intragastrik gavaj yoluyla verildi.

3. Grup (*Nigella sativa L.* grubu): Birinci gün *Nigella sativa L.* ekstraktı intragastrik gavaj yoluyla verildikten 24 saat sonra 7 adet sıçan uyutuldu ve geri kalan 7 adet sıçana 28 gün boyunca günlük %5'lik CMC çözeltisi içerisinde hazırlandı. *Nigella sativa L.* ekstraktı 300 mg/kg/gün dozda olmak üzere intragastrik gavaj yoluyla verildi.

4. Grup (Metil paratiyon + *Nigella sativa L.* grubu): Birinci gün metil paratiyon ve 2 saat sonra *Nigella sativa L.* ekstraktı ağız yoluyla verildi, 24 saat sonra 7 adet sıçan uyutuldu ve geri kalan 7 adet sıçana 28 gün boyunca ağızdan günlük 0,28 mg/kg (1/50 LD 50) dozunda mısır özü yağı içinde çözülmüş metil paratiyon ve 2 saat sonrasında %5'lik Na-CMC çözeltisinde çözdürülen *Nigella sativa L.* ekstraktı 300 mg/kg/gün dozda intragastrik gavaj yoluyla verildi.

Örneklerin ve dokuların toplanması

Birinci gün uygulamasından 24. saat ve 28. gün uygulama gruplarında yer alan 7 adet sıçanın anestezi altında kalplerinin sol ventrikülünden serum tüplerine kan alındı. Kanlar 3000 devirde +4 C'de 10 dakika santrifüj edildi ve elde edilen serumlar analizlere kadar -20 ^{o}C'de saklandı. Toplam antioksidan seviye (TAS), toplam oksidan seviye (TOS), antioksidan vitaminler (A, C ve E) ve biyokimyasal parametreler elde edilen serumlarda analiz edildi.

Yapılan analizler

Toplam antioksidan seviye (TAS) ve toplam oksidan seviye (TOS) analizi: Toplam antioksidan/oksidan seviye, rel assay ticari kitleri ile analiz edildi (Erel, 2004; Erel, 2005). Analiz öncesi serum örnekleri, oda ısısına getirildi. TAS ve TOS düzeyi, Van YYÜ Veteriner Fakültesi Biyokimya Laboratuvarında Eliza cihazında (Anthos zenyth 200rt) kolorimetrik olarak analiz edildi.

Vitamin A ve vitamin E'nin HPLC'de analizi: Analiz öncesi oda ısısına getirilen serumlar ve Vitamin A ve Vitamin E analizleri için 200 µL serum plastik tüplere aktarıldı. Üzerine 200 µL etanol eklenerek 1 dakika süre boyunca vorteks cihazıyla karıştırıldı. 800 µL n-hekzan eklendi ve tekrardan 1 dakika süre ile vorteks cihazı ile karıştırıldı ve 2000 rpm'de 10 dakika boyunca santrifüje edildi. Oluşan hekzan fazından 600 µL alındı ve azot gazı altında kurutulma işlemi yapıldı. Oluşan kalıntı 500 µL metanol içerisinde çözdürüldü ve 20 µL viyollere alınarak analiz için kullanıldı. Serum Vitamin A ve Vitamin E düzeyleri; Van YYÜ Bilimsel Araştırma Merkez Laboratuvarı'nda Termo marka HPLC ile analiz edildi. Standart olarak, vitamin A ve vitamin E standartları kullanıldı. Hazırlanan ekstraktlar, HPLC viyallerine aktarıldı. Kromatografinin otosamplerından 20 µL alındı ve sıvı kromatografisi kolonuna enjekte edildi. Vitamin A ve Vitamin E analizleri, 325 ve 290 nm dalga boylarında Diode-Array Detector (DAD) yapıldı. Mobil faz olarak, metanol-su (98:2) karışımı, 1.5 mL/dk akış hızına ayarlandı. C18 HPLC kolonu (4,6 mm x 25 cm) kullanıldı. Hesaplamalar vitamin A ve vitamin E düzeyleri, standartlarının pik alan ve konsantrasyonlarına göre hesaplandı (Zaspel ve ark., 1983).

Vitamin C (Dinitrofenilhidrazin ile) kolorimetrik analizi: Serum vitamin C analizi için oda ısısında getirilen 0.4 mL serum üzerine 1.6 mL %10 triklorasetik asit kondu. İyice karıştırıldıktan sonra 5 dakika bekletildi ve 2000 devirde santrifüj edildi. Test tüpüne 1 mL filtrat alındı ve üzerine 0.4 mL dinitrofenilhidrazin (DNPH) ayıracı ilave edildi. Tüpün ağzı kapatılarak 37 ^{o}C'de 3 saat inhibe edildi. Buz içinde soğutuldu ve 1.6 mL soğuk %65 H_2SO_4 kondu ve iyice karıştırıldı. Oda ısısında 30 dakika bekletildi. Blenk 1 mL %10 TCA ile kan serumu gibi hazırlandı. Standart ise 0.4 mL %1 mg'lık askorbik asit çözeltisi ile serumun tabi tutulduğu işleme tabi tutularak hazırlandı (Akkuş, 2007). Vitamin C düzeyi; Van YYÜ Veteriner Fakültesi Biyokimya Laboratuvarında Eliza cihazında (Anthos Zenyth 200rt) kolorimetrik olarak analiz edildi.

Biyokimyasal parametrelerin analizleri: Serum toplam protein, albumin, ALT, AST, ALP, GGT, LDH, toplam trigliserit, toplam kolesterol, VLDL kolesterol düzeyleri Van YYÜ Dursun Odabaş Tıp Merkezi Biyokimya Laboratuvarında kitle otoanalizör cihazında kolorimetrik olarak analiz edildi.

Histopatolojik analizler: Metil paratiyon ve *Nigella sativa L.* ekstraktının deneme gruplarına uygulamasından 24 saat ve 28 gün sonra, her gruptan 7'er sıçan karaciğeri histopatolojik değişiklikler açısından incelendi. Uygulamadan 24 saat ve 28. gün sonraki gruplarda yer alan sıçanların karaciğerleri anestezi altında formaldehid içeren doku kaplarına alındı. Histopatolojik inceleme için alınan karaciğer dokuları, %10'luk formalin'de 48-72 saat tespit sonrasında, çeşme suyu ile 6-8 saat yıkama işlemine alındı. Rutin dokuların takibinde alkol (70°, 80°, 90°, 96° ve 100°) ve ksilol serilerinden geçirildikten sonra parafinde bloklandı. Bloklardan 4 µm kalınlığında kesitler alındı. Histopatolojik inceleme amaçlı alınan kesitler hematoksilen-eozin ile boyandıktan sonra ışık mikroskobunda incelendi.

İstatistik analiz

Çalışma sonucunda elde edilen tanımlayıcı istatistikler; ortalama ve standart sapma olarak ifade edildi. Deneme gruplarının karşılaştırılmasında Kruskal-Wallis testi kullanıldı. Farklı grupları belirlemede, Tukey çoklu karşılaştırma testi kullanıldı. 24. saat ile 28. gün arasında fark olup olmadığını belirlemek amacıyla gruplarda ayrı ayrı olmak üzere Wilcoxon testi yapıldı. Hesaplamalarda istatistik anlamlılık düzeyi $p<0,05$ olarak alındı ve hesaplamalar için SPSS istatistik paket programı (13.0) kullanıldı.

BULGULAR

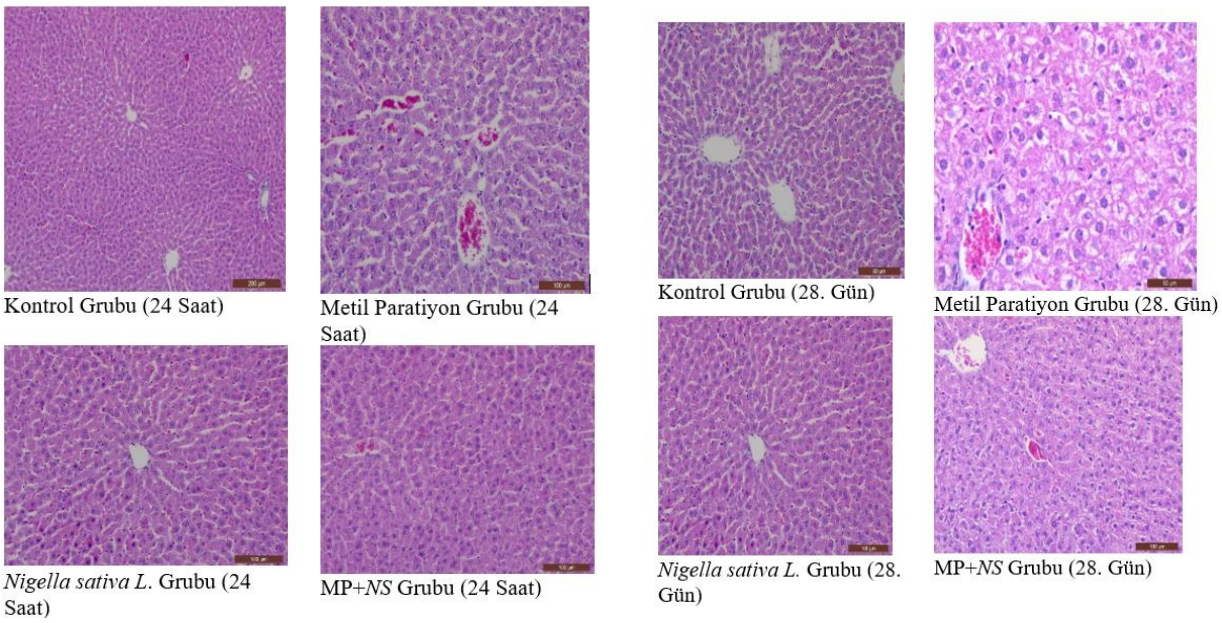
Tablo 1'de serum TAS düzeyleri; 24 saat ve 28. gün sonra düzeylerinin incelenmesinde gruplar arasında istatistiksel olarak anlamlı bir farkın olmadığı tespit edilmiştir (p>0.05). Metil paratiyon uygulanan grup 2'de serum aspartat aminotransferaz (AST), alanin amino transferaz (ALT), alkalin fosfataz (ALP) ve toplam kolesterol diğer gruplara göre (özellikle grup 4) istatistiksel olarak anlamlı bir artış olduğu aynı zamanda serum albumin ve vitamin E düzeylerinde istatistiksel olarak anlamlı azalma olduğu tespit edilmiştir (p<0.05). Ayrıca, laktat dehidrogenaz (LDH), gama glutamil transferaz (GGT), VLDL kolesterol ve toplam oksidan kapasite düzeylerinde artış olduğu ancak bu artışın istatistiksel olarak anlamlı olmadığı tespit edilmiştir (p>0.05). Grup 2'de serum toplam protein, toplam trigliserid, toplam antioksidan kapasite, vitamin A ve C düzeylerinde azalma olduğu ancak bu azalmanın istatistiksel açıdan anlamlı olmadığı tespit edilmiştir (p>0.05).

Tablo 1. Deneme gruplarının 24. saat ve 28. gün serum biyokimyasal parametre düzeyleri

		Kontrol (S±SD)	**Metil Paratiyon (S±SD)**	***Nigella sativa L.* (S±SD)**	**MP+*NS L.* (S±SD)**
TAS (mmol/L)	24 Saat	1,25±0,68	0,96±0,26	1,28±0,52	1,18±0,59
	28. Gün	0, 96±0,58	0,69±0,36	0,97±0,41	0,95±0,09
TOS (µmol/L)	24 Saat	9,95±0,76	11,39±1,64	8,18±1,52	10,13±3,61
	28. Gün	6,65±1,30	8,91±1,53	5,19±3,52	7,78±0,84
A vitamini (ug/mL)	24 Saat	0,52±0,05^{ab}	0,34±0,20^{ab}	0,42±0,22^{b}	0,56±0,13^{a}
	28. Gün	0,59±0,28^{b}	0,57±0,30^{ab}	0,89±0,17^{a}	0,88±0,33^{a}
E vitamini (ug/mL)	24 Saat	1,61±0,12^{a}	0,57±0,29^{b}	0,50±0,22^{b}	0,77±0,20^{b}
	28. Gün	1,46±0,32^{b}	0,69±0,30^{ab}	0,87±0,23^{a}	0,93±0,33^{a}
C vitamini (ug/mL)	24 Saat	0,16±0,04	0,11±0,03	0,13±0,03	0,16±0,09
	28. Gün	0,16±0,11	0,12±0,01	0,11±0,03	0,13±0,03
AST (U/L)	24 Saat	120,17±26,39^{ab}	160,80±66,87^{a}	115,29±24,69^{ab}	108,20b±10,40^{b}
	28. Gün	92,86±13,12^{a}	96,20±19,02^{a}	92,80±9,31^{a}	93,75±6,95^{a}
ALT (U/L)	24 Saat	33,80±1,64^{ab}	35,50±2,89^{a}	31,60±1,14^{a}	30,60±3,65^{b}
	28. Gün	39,83±5,27^{a}	43,40±4,62^{a}	39,57±2,57^{a}	41,86±5,18^{a}
GGT (U/L)	24 Saat	1,63±0,98^{a}	2,70±0,85^{a}	1,97±0,70^{a}	1,96±1,00^{a}
	28. Gün	2,07±0,69^{ab}	2,95±1,41^{a}	1,23±0,54^{b}	2,22±0,94^{ab}
LDH (U/L)	24 Saat	1018,83±529,77	1286,6±377,93	1133,2±375,69	903,00±219,20
	28. Gün	755,20±218,93	831,80±208,55	688,33±173,19	805,20±128,35
ALP (U/L)	24 Saat	260,50±34,04^{a}	260,60±39,87^{ab}	207,33±53,56^{b}	271,75±32,91^{a}
	28. Gün	247,17±65,60^{ab}	327,33±101,35^{a}	213,57±65,22^{b}	222,80±25,58^{b}
Albumin (g/dL)	24 Saat	3,13±0,21^{a}	2,95±0,05^{b}	3,10±0,06^{a}	3,17±0,08^{a}
	28. Gün	3,17±0,17^{a}	3,02±0,08^{a}	3,01±0,09^{ab}	3,07±0,16^{b}
Kolesterol (mg/dL)	24 Saat	61,20±7,92^{a}	63,00±7,78^{a}	56,29±8,83^{a}	62,14±12,64^{a}
	28. Gün	50,67 ±5,50^{ab}	63,00±5,24^{a}	56,67±5,50^{ab}	51,00±6,56^{b}
VLDL-Kolesterol (mg/dL)	24 Saat	12,96±2,75^{b}	14,05±1,23^{a}	14,05±1,23^{a}	13,00±3,66^{a}
	28. Gün	17,60±5,62^{a}	17,20±6,13^{a}	18,29±3,74^{a}	12,69±3,93^{a}
Trigliserit (mg/dL)	24 Saat	70,86±16,49	63,20±11,90	77,17 ±9,06	65,40±16,09
	28. Gün	96,83±23,38	73,60±17,04	91,43±18,69	76,75±12,09
T. Protein (mg/dL)	24 Saat	6,13±0,23	5,78±0,29	6,17±0,15	6,07±0,23
	28. Gün	6,14±0,23	5,93±0,21	6,17±0,26	6,00±0,29

Satırlar arasında farklı harfler istatistik açıdan önemlidir (p<0.05).

*: Aynı sütunda farklı küçük harfi olan grup ortalamaları arasındaki fark anlamlıdır (p<0.05).



Şekil 1. Deneme gruplarının 24. saat ve 28. gün karaciğer dokusu histopatolojik bulguları

Şekil 1'de Deneme gruplarına ait 24 saat sonraki Karaciğer dokularının ışık mikroskobunda histopatolojik incelenmesinde; kontrol grubu ve *Nigella Sativa L.* grubu karaciğer dokuları normal histolojik yapıda tespit edildi. Metil paratiyon grubuna ait karaciğer dokularının histopatolojik incelenmesinde, hepatositlerin şişkin, sitoplazmalarının bulanık ve granüler görünümde oldukları, sitoplazma membranlarının yer yer ortadan kalktığı, hücre yapılarının normal yapısının bozulduğu, sinüzoidlerde konjesyon durumunun belirgin olduğu tespit edildi. Metil paratiyon+*Nigella sativa L.* grubunda karaciğer dokularının histopatolojik incelenmesinde ise bulgular metil paratiyon grubuyla aynı olmakla birlikte ancak lezyonların şiddetinin metil paratiyon grubuna göre biraz daha hafif olduğu gözlendi.

Şekil 1'de Deneme gruplarına ait 28 gün sonraki Karaciğer dokularının ışık mikroskobunda histopatolojik incelenmesinde; kontrol grubu ve *Nigella Sativa L.* grubu karaciğer dokuları normal histolojik yapıda tespit edildi. Metil paratiyon grubuna ait karaciğer dokularının hisyopatolojik incelenmesinde; hepatositlerin şişkin, sitoplazmalarında çok şiddetli hidropik dejenerasyon gözlenmekte hepatosit kordonlarının düzeninin bozulduğu ve sinüzoidlerde konjesyon durumunun belirginleştiği tespit edildi. Metil paratiyon+*Nigella sativa L.* grubunda karaciğer dokularının histopatolojik incelenmesinde ise; bulgular metil paratiyon grubuyla aynı olmakla birlikte lezyonların şiddeti daha hafif, bazı kesitlerin portal alanlarında hafif mononükleer hücre infiltrasyonu gözlendi.

TARTIŞMA

Bu çalışmada; metil paratiyonun sıçan karaciğeri üzerine akut ve kronik toksisitesi biyokimyasal ve histopatolojik olarak değerlendirilerek ortaya konulmaya çalışılmış ve metil paratiyondan kaynaklı karaciğer toksisitesi üzerine *Nigella sativa L.* ekstraktının iyileştirici etkisi araştırılmıştır.

Çalışmada serum TAS düzeyleri; 24 saat ve 28. gün sonra düzeylerinin incelenmesinde, grupların istatistik analizinde gruplar arası farklılık bulunamamıştır ($p>0.05$). Metil paratiyon verilen grupta TAS düzeyi aritmetik olarak en düşük düzeyde, *Nigella sativa L.* grubunda ise en yüksek düzeyde tespit edilmiştir. 28. Gün verilerinin birbirlerine aritmetik olarak daha yakın olduğu görülmektedir. Metil paratiyon+*Nigella sativa L.* grubunda ise ekstrakt verilmesi sonrası verilerin aritmetik olarak kontrol grubu verilerine yaklaştığı tespit edilmiştir. Ayrıca serum TOS düzeyleri; 24 saat ve 28. gün sonra düzeylerinin incelenmesinde grupların istatistik analizinde gruplar arası farklılık bulunamamıştır ($p>0.05$). TOS düzeylerinin aritmetik olarak 24 saat sonra *Nigella sativa L.* grubunda en düşük düzeyde, metil paratiyon grubunda ise en yüksek düzeyde olduğu görülmektedir. Ancak *Nigella sativa L.* ekstraktı uygulanması ile TOS düzeyinin tamamen olmasa da kısmi olarak iyileşmeye kontrol grubu verilerine yaklaştığı görülmektedir.

Metil paratiyonun nefrotoksik etkisinin araştırıldığı çalışmada, metil paratiyon uygulanması sonucu, vücut ve böbrek ağırlığında önemli ölçüde azalma, böbrek dokusunda lipit peroksidasyon göstergesi malondialdehit (MDA) düzeyinde artış saptanmıştır (Kalender ve ark., 2007).

Organofosfatlı insektisitlerin biyolojik sistemlerde serbest radikal artışına neden oldukları, dokularda ve biyolojik sistemlerde serbest radikal üretimi sonucu oksidatif hasar oluşturduğu ve lipid peroksidasyonuna yol açtığı tespit edilmiştir (Hazarika ve ark., 2003; Vidyasagar ve ark., 2004; Verma ve ark., 2007).

Karbontetraklorür (CCl_4)'ün oluşturduğu karaciğer fibrozisinin engellenmesinde *Nigella sativa L.*'nın rolünün araştırıldığı çalışmada, MDA düzeyleri CCl_4'ün neden olduğu hepatotoksik sıçanlarda kontrol grubu ile karşılaştırma yapıldığında istatistik olarak yüksek bulunmuştur ($p<0.05$). Ortalama eritrosit SOD ve GPx düzeyleri CCl_4'ün indüklediği grupta kontrol grubu ile karşılaştırıldığında istatistiksel olarak düşük olduğu görülmüş ve *Nigella sativa L.* tedavisinden sonra bu düzeylerin istatistiksel olarak arttığı tespit edilmiştir (İlhan ve Seçkin, 2005). El-Saleh ve ark. (2004), sıçanlarda *Nigella sativa L.* yağını uyguladıkları çalışmalarında, TAS düzeyinde önemli oranda artış tespit etmişlerdir.

Araştırmada, serum TAS ve TOS düzeylerinde metil paratiyon uygulanması sonrası istatistiksel olarak önemli bir farklılık bulunamamasına rağmen aritmetik olarak metil paratiyon verilen grupta TAS düzeyinde düşüş, TOS düzeyinde artış tespit edilmiştir. Yukarıda pestisitlerin etkileri ile ilgili yapılan çalışmalarda, pestisit uygulanan gruplara ait antioksidan enzim, TAS düzeylerinde artış, lipid peroksidasyon ürünü MDA ve TOS düzeylerinde azalma olduğu bildirilmekte, bizim çalışmamızda elde edilen serum TAS ve TOS düzeyleri yapılan bu çalışmalarla uyum gözlenmiştir.

Çalışmada elde edilen serum vitamin A, C ve E düzeyleri; 24 saat ve 28. gün sonrası metil paratiyon uygulanan grupta aritmetik olarak en düşük düzeyde tespit edilmiştir. E vitamini düzeyleri 28. Gün sonrası metil paratiyon grubunun kontrol grubuna göre istatistiksel olarak önemli oranda düştüğü tespit edildi ($p<0.05$). Metil paratiyon grubundaki vitamin düzeylerindeki (A ve C) düşüşler aritmetik düzeyde kalmıştır. Metil paratiyon nedenli hasara karşı koruyucu amaçla *Nigella sativa L.* ekstraktı verilen grupta vitamin düzeylerinde aritmetik olarak artış saptandı.

Deneysel diyabet oluşturulan sıçanlarda, katalaz, glutatyon-S-transferaz (GST), glutatyon peroksidaz (GPx) gibi antioksidan enzim ile vitamin C ve vitamin E düzeylerini önemli ölçüde azaldığı, *Nigella sativa L.*'nın uygulanması sonucunda antioksidan enzim ve vitamin düzeylerinde artış olduğu belirtilmiştir (Sankaranarayanan ve Pari, 2011). Yine benzer şekilde deneysel diyabet oluşturulan sıçanlarda likopenin koruyucu etkisinin araştırıldığı çalışmada, diyabet grubunda kontrol grubuna göre istatistiksel olarak TAS, Vitamin A ve Vitamin E düzeylerinin azaldığı tespit edilmiştir (Yüztaş ve ark., 2014).

Çalışmada elde edilen serum karaciğer enzim düzeylerinin incelenmesinde, metil paratiyon uygulamasından 24 saat sonrasında serum AST ve ALT düzeylerinde; metil paratiyon uygulamasıdan 28 gün sonrasında serum ALP düzeylerinde gruplar arasında istatistiksel açıdan anlamlılık tespit edilmiştir ($p<0.05$). Çalışmada metil paratiyon uygulamasının 24 saat ve 28 gün sonrasında, metil paratiyon uygulanan gruba ait serum karaciğer enzim düzeyleri (GGT, LDH) aritmetik olarak artmıştır. Serum karaciğer enzimlerinde artışlar 24 saat sonrasında daha belirgin düzeydedir. Metil paratiyon+*Nigella sativa L.* ekstraktı verilen gruptaki serum karaciğer enzim düzeylerinin metil paratiyona göre daha az yükseldiği, *Nigella sativa L.*'nın karaciğer iyileştirici etkisini ortaya koyduğu kanaatindeyiz.

Yang ve Deng (2007) çalışmalarında CCl_4 ile oluşturulan toksisite sonrasında AST, LDH ve ALT düzeylerinin 24 saat içinde anlamlı bir şekilde arttığını bildirmişlerdir. Mansour ve ark. (2001), CCl_4 ile oluşturdukları karaciğer hasarına karşı *Nigella sativa L.*'nın aktif bileşeni timokinonun etkisini araştırmışlar, tek doz CCl_4 uygulanan grupta karaciğer enzimleri AST, ALT ve LDH değerlerinde anlamlı bir artış, timokinon enjekte edilen grupta, serum enzim düzeylerinde anlamlı bir azalma olduğunu bildirmişlerdir.

Yıldız ve arkadaşları (2006), yaptıkları çalışmada metil paratiyon uygulanan sıçanların plazma laktat dehidrojenaz (LDH) enzim aktivitesinde metil paratiyon uygulanan grup ile kontrol grubu arasında istatistiksel bir fark olmadığını tespit etmişlerdir. Nagi ve arkadaşları (2010), çalışmalarında Asitaminofen nedenli hepatotoksisitenin önlenmesinde timokinonun ağız yoluyla uygulanması ile serum ALT aktivitesinde düşüş kaydedilmiştir.

Sayed-Ahmed ve ark. (2010), deney hayvanlarına dietilnitrozamin uygulandıkları çalışmada sonrası karaciğerde ALT ve ALP aktivitelerinde artış saptamışlar ve timokinon uygulaması ile karaciğerde bu enzim düzeylerinde düzelme tespit etmişlerdir. Altuntas ve Delibas (2002), albino sıçanlara organofosfatlı bir insektisit fenthion uygulamasının lipid peroksidasyonu ve karaciğer enzimlerinden ALP, AST, LDH ve GGT seviyelerini önemli ölçüde artırdığını, ALT aktivitelerini önemli ölçüde azalttığını tespit etmişlerdir. Meral ve ark. (2001), Deneysel diyabet oluşturulan tavşanlarda *Nigella sativa* tedavisinin lipid peroksidasyonunu önlediğini, antioksidan savunma sisteminin aktivitesini arttırdığını ve karaciğer hasarından koruduğunu tespit etmişlerdir.

Çalışmadaki metil paratiyon uygulaması sonrası serum karaciğer enzim düzeylerindeki artışlar, yukarıda bildirilen karaciğer hasarı üzerine yapılan çalışmalardaki sonuçlarla paralellik arz etmektedir.

Çalışmadaki serum toplam kolestrol düzeyleri 24 saat sonra metil paratiyon ve metil paratiyon+*Nigella sativa L.* grubunda aritmetik olarak yüksek düzeyde olduğu görülürken 28. günün sonunda en yüksek düzeyin metil paratiyon grubunda olduğu saptandı. Metil paratiyon grubu toplam kolesterol düzeyi 28. gün verilerinin metil paratiyon+*Nigella sativa L.* uygulanan grup arasında istatistiksel olarak önemlilik söz konusudur ($p<0.05$).

Çalışma serum VLDL kolestrol düzeylerinde 24 saat sonra metil paratiyon uygulanan grupta kontrol grubuna göre artış istatistiksel olarak önemli bulunmuştur ($p<0.05$). Yalnız MP+NS grubuna göre istatistiksel açıdan farklılık yoktur. Metil paratiyon uygulaması sonrası *Nigella sativa L.* ekstraktı verilmesi serum VLDL kolesterol düzeyini kontrol grubu verilerine yaklaştırmıştır. Serum VLDL-kolesterol düzeylerinin 28. gün verilerinde gruplar arasında istatistiksel açıdan bir farklılık tespit edilememiştir $p>0.05$).

Serum trigliserit düzeylerinde 24. saat ve 28. gün verileri arasında istatistiksel olarak bir farklılık bulunamamıştır ($p>0.05$). Serum trigliserit düzeylerinin 24. saat ve 28. gün verilerinin incelenmesinde metil paratiyon grubunda en düşük düzeyde olduğu saptanmıştır. Metil paratiyon sonrası *Nigella sativa L.* uygulanan grubun kontrol grubuna doğru yaklaştığı tespit edilmiştir.

Öğütcü ve ark. (2008), organofosfatlı insektisitlerin toplam lipid ve toplam kolesterol seviyelerinde artışa neden olduğu belirtilmiştir. Uzunhisarcikli ve Kalender (2011), yaptıkları bir çalışmada pestisit maruziyeti sonucu karaciğerde lipid metabolizmasının bozulduğunu ve serum kolesterol düzeyinin arttığını tespit etmişlerdir. Joshi ve ark. (2003), yaptıkları çalışmada, 30 mg/kg dozunda metil paratiyon uygulaması sonucu sıçanlarda serum toplam kolesterol ve trigliserit düzeyinin arttığını bildirmişlerdir. Deneysel olarak hiperkolesterolemi oluşturulmuş sıçanlarda, *Nigella sativa L.* uygulanmasının, plazma toplam kolesterol ve LDL kolesterol düzeylerinin önemli oranda azalttığı tespit edilmiştir (Ismail ve ark., 2010).

Timokinon uygulanmasının kandaki lipid yapılı bileşikler üzerine etkilerinin araştırıldığı çalışmada; serum toplam kolesterol, LDL kolesterol ve trigliserit seviyelerinin azaldığı bildirilmiştir (El-Dakhakhny ve ark., 2000). Kolesterolden zenginleştirilmiş diyetlere koruyucu olarak timokinon ilave edildiği çalışmada; trigliserit, toplam kolesterol düzeylerinin sadece kolesterol verilen grupta arttığı, timokinon verilen gruplarda ise serum toplam kolesterol ve LDL kolesterol düzeylerinin azaldığı bildirilmiştir (Ragheb ve ark., 2008). Sıçanlarda yapılan bir çalışmada timokinonun; trigliserit, kolesterol düzeylerini azalttığı saptanmıştır (Bamosa ve ark., 2002).

Çalışma serum albümin düzeylerin 24 saat sonra metil paratiyon uygulanan grubun diğer gruplarla karşılaştırılmasında istatistiksel olarak anlamlı bir düşüş saptanırken ($p<0.05$), 28. gün sonunda verilerinin incelenmesinde bu düşüş aritmetik düzeyde kalmıştır ($p>0.05$). Serum toplam protein düzeylerinde 24. saat ve 28. gün verileri incelendiğinde metil paratiyon uygulanan grupta diğer gruplara nazaran aritmetik bir düşüş gözlenmiş olup, metil paratiyon sonrası *Nigella sativa L.* verilen grupta anlamlı bir yükseliş görüldü. MP+NS grubunda toplam protein düzeyleri kontrol grubuna aritmetik olarak yakın değerler tespit edilmiştir.

Pestisitlere maruz kalan hayvanlarda plazma proteininde azalma olduğu tespit edilmiş ve bu azalmanın karaciğer fonksiyonundaki düzensizlik nedeniyle meydana geldiği öngörülmüştür (Uzunhisarcıklı ve Kalender, 2011).

Çalışmada 24 saat sonraki karaciğer dokularının histopatolojik incelenmesinde; hepatositlerin şişkin, sitoplazmalarının bulanık ve granüler görünümde oldukları, sitoplazma membranlarının yer yer ortadan kalktığı, hücre yapılarının normal yapısının bozulduğu, sinüzoidlerde konjesyon durumunun belirgin olduğu tespit edildi. 28 gün sonraki Karaciğer dokularının histopatolojik incelenmesinde; kontrol grubu ve *Nigella sativa L.* grubu karaciğer dokuları normal histolojik yapıda tespit edildi. Metil paratiyon grubuna ait karaciğer dokularında hepatositlerin şişkin, sitoplazmalarında çok şiddetli hidropik dejenerasyon, hepatosit kordonlarının düzeninin bozulduğu ve sinüzoidlerde konjesyon durumunun belirginleştiği tespit edildi.

Dimethoatın etkisinin incelendiği bir çalışmada, dimethoat muamelesi yapılan sıçanların karaciğerinde hepatositlerde şişme, hepatositlerde bölgesel nekroz, portal inflamasyon ve yağlı değişime sebep olduğunu gözlemişlerdir (Sharma ve ark., 2005). Kalender ve ark. (2005) Diazinon uygulanan gruplarda hepatositlerin endoplazmik retikulumlarında ve mitokondrilerinde şişme, çekirdeğin kromatin yoğunluğunda kayıp ve mitokondriyal kristalarda kırılmalar olduğu gözlenmiştir. Tripathi ve Srivastav (2010), Organofosfatlı pestisit olan klorprifosla yaptıkları çalışmada sıçanların karaciğerinde hepatositlerde dejenerasyon, hepatik vakuolizasyon, hiperkromatik ve hipertrofi olmuş çekirdek, kupffer hücrelerin sayısında artış, fokal nekroz ve sinuzoidal dilatasyon şeklinde histopatolojik değişimler görülmüştür. Yalçın ve ark. (2020), sıçanlarda Siklofosfamid uygulamasının karaciğerde konjesyon, ödem, dejenerasyon ve nekroz oluşumuna neden olduğunu tespit etmişlerdir.

Turkdogan ve arkadaşları (2003), *Nigella sativa L.*'nin CCl_4 hepatotoksisitesine karşı koruyucu etkisini araştırmış, CCl_4 muamelesi yapılan grupta periasinar bölgelerde koagülasyon nekrozu hidropik dejenerasyon ve portal kanallarda fibröz görülmüştür. CCl_4 ile *Nigella sativa L.* sabit yağı ve CCl_4 ile *Nigella sativa L.* uçucu yağı ile muamele edilen gruplarda periasinar bölgelerde seyrek nekroz koagülasyonu dışında ciddi histopatolojik bulguların hiçbiri saptanmamıştır. Berköz ve ark. (2019), *Nigella sativa L.* ekstraktının Metil Paratiyonun neden olduğu karaciğer hasarında antiinflamatuar ve antioksidatif fonksiyonu olduğunu tespit etmişlerdir. Karsinojenik bir bileşik olan dietilnitrozamin uygulandıktan sonra karaciğerde histopatolojik olarak hasar meydana gelmiştir, buna karşın *Nigella sativa L.*'dan izole edilen timokinonun uygulanmasından sonra karaciğerde meydana gelen bütün histopatolojik değişiklikleri geri çevirdiği ve kontrole yaklaştırdığı tespit edilmiştir (Sayed-Ahmed ve ark., 2010).

Çalışmada metil paratiyon ve *Nigella sativa L.* uygulaması sonrası karaciğer dokusunda meydana gelen değişiklikler yukarıda bildirilen çalışma sonuçları ile paralellik arz etmektedir.

Sonuç olarak; çalışmamızda deney hayvanlarına literatürdeki veriler referans alınarak, metil paratiyonun uygulama dozu olarak 1/50 LD_{50} dozu belirlenmiş, 0.28 mg/kg verilmiştir. Metil paratiyon hasarına karşı *Nigella sativa L.* ekstraktı verilen gruplarda metil paratiyon hasarına karşı bütün parametrelerdeki artma ve azalmalara karşı iyileştirici etkiler tespit edilmiştir. Bu etkiler, karaciğerin akut ve kronik histopatolojisinde daha belirgin olarak görülmüştür. Çalışmada metil paratiyon uygulaması sonrasında *Nigella sativa L.* ekstraktının iyileştirici etkisi açık ve belirgin bir şekilde tespit edilmiştir.

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Ağız, Diş ve Çene Cerrahisi ile Periodontoloji Alanlarında Uzmanlık veya Doktora Eğitimi Almakta Olan veya Eğitimi Tamamlamış Diş Hekimlerinin Atık Yönetimi Bilgi Düzeylerinin Karşılaştırılması

Comparison of Waste Management Knowledge Levels Among Dentists Who are Currently Pursuing or Have Completed Specialty or Doctoral Education in Oral and Maxillofacial Surgery, and Periodontology

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ABSTRACT

Objective: In dentistry clinics/polyclinics; biological medical waste and general waste are generated. In order to separate these wastes and send them to appropriate disposal or recycling units, doctors must have a good level of waste knowledge. The aim of this study is to determine and compare the waste knowledge levels of research assistants and specialists /dentist with PhD degrees at oral and maxillofacial surgery and periodontics working in dental clinics/polyclinics.

Material and Method: The study was conducted with data collected through an online survey platform for dentists with specialists/PhD degrees at periodontics and oral surgery working in university or private oral and dental health center/hospital clinics and research assistants continuing their education. Four groups were used in the study and the surveys were filled out by 80 people, the 20 participants in each group. The level of statistical significance was accepted as 5% in data evaluation and SPSS (ver:21) statistical package program was used for calculations.

Results: According to gender, working period, education level and title; no significant difference was found in the evaluation of waste knowledge levels of individuals participating in the study.

Conclusion: As a result, specialists/ dentist with PhD degrees who have received these trainings are expected to have the highest level of waste knowledge. For this reason, all dentists, regardless of their branch, should update their knowledge about waste periodically.

Keywords: *Knowledge, Maxillofacial surgery, Medical waste, Periodontics*

ÖZET

Giriş: Diş hekimliği klinik/polikliniklerinde; biyolojik tıbbi atıklar ile genel atıklar ortaya çıkar. Bu atıkların ayrıştırılması ve uygun bertaraf veya geri dönüşüm birimlerine gönderilmesi için hekimlerin iyi derecede atık bilgisine sahip olmaları gereklidir. Bu çalışmanın amacı, diş klinik/polikliniklerde çene cerrahisi ve periodontoloji uzman/doktoralı diş hekimlerinin ve asistanlarının atık bilgi düzeylerinin belirlenmesi ve karşılaştırılmasıdır.

Materyal ve Metot: Çalışma; üniversite veya özel ağız ve diş sağlığı merkezi/hastanesi kliniklerinde çalışan periodontoloji ve çene cerrahisi uzman/doktoralı diş hekimleri ile bu eğitimlerine devam eden asistanlara yönelik yapılan çevrimiçi bir anket platformu aracılığıyla toplanan veriler ile yapılmıştır. Çalışmada dört grup kullanılmış ve anketler her grupta 20'şer kişi olmak üzere 80 kişiye doldurtulmuştur. Değerlendirmelerde istatistik anlamlılık düzeyi %5 olarak alınmış ve hesaplamalar için SPSS (ver:21) istatistik paket programından yararlanılmıştır.

Bulgular: Çalışmaya katılan bireylerin; cinsiyet, çalışma süresi, eğitim derecesi ve unvanlarına göre atık bilgi düzeylerinin değerlendirilmesinde anlamlı farklılık bulunmamıştır.

Sonuç: Sonuç olarak, uzman/doktoralı diş hekimleri ya da bu eğitimleri alan diş hekimlerinin atık bilgi düzeylerinin en üst seviyede olması beklenir. Bu sebeple hangi branş olursa olsun tüm diş hekimleri zaman zaman atıklar konusunda bilgilerini güncellemelidir.

Anahtar kelimeler: *Bilgi, Maksillofasiyal cerrahi, Periodontoloji, Tıbbi atık*

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GİRİŞ

Diş hekimliği klinik/polikliniklerinde; tedavi işlemlerinde biyolojik tıbbi atıklar ile tedavi dışı klinik işleyişlerin sonucunda genel atıklar ortaya çıkar (Schaefer, 1991; Kapoor ve ark., 2014; WHO, 2014). Tedavi işlemlerinde infeksiyöz atıklar, patolojik atıklar, kesici atıklar, farmasötik atıklar vb. tehlikeli ve tıbbi atıklar ortaya çıkarken tedavi dışındaki işleyişte ise organik atık, cam atık, kâğıt atık vb. atıklar birikir (Schaefer, 1991; WHO, 2014). Bu atıklar birbirleriyle karışırlarsa karışımdaki en tehlikeli atık çeşidi olarak değerlendirilmelidirler (Akbolat ve ark., 2011; Tıbbi Atıkların Kontrolü Yönetmeliği, 2017).

Atıkların klinik/polikliniklerde ayrıştırılması ve uygun bertaraf veya geri dönüşüm birimlerine gönderilmesi gerekir (Monica ve ark., 2022). Bu ayrımın yapılabilmesi için hekimlerin çok iyi derecede atık bilgisine sahip olmaları ve birlikte çalıştıkları kişileri eğitmeleri veya eğitim almalarını sağlamalı ve denetlemeleri gereklidir (Mehta ve ark., 2013; Dhar ve ark., 2018; Subramanian ve ark., 2020). Düzgün işletilmeyen bir atık yönetimi hem sağlık ekibi hem hastalar hem de halk için büyük risk oluşturur (Dhar ve ark., 2018; Khubchandani ve ark., 2020). Ne yazık ki hem tıp hem de diş hekimliği ile ilgili tedavi merkezlerinde geri dönüşüm ve tıbbi atıklar yerel çöp kutularına ve çöp sahalarına atılabilmektedir (Khatri ve ark., 2014).

Bu çalışmanın amacı, diş klinik/polikliniklerde daha fazla zararlı atık üretme potansiyeline sahip ağız, diş çene cerrahisi ve periodontoloji birimlerinde çalışan uzman/doktoralı diş hekimlerinin veya asistanlarının atık bilgi düzeylerinin belirlenmesi ve karşılaştırılması ile eğitim ihtiyacının var olup olmadığının tespit edilmesidir.

MATERYAL ve METOT

Çalışma; ülkemizdeki kamu veya özel üniversite, özel veya kamu ağız ve diş sağlığı merkezi/hastanesi kliniklerinde çalışan periodontoloji ve çene cerrahisi bölümleri uzman/doktoralı diş hekimleri ile üniversitelerde öğrenim gören periodontoloji ve çene cerrahisi uzmanlık veya doktora eğitimlerine devam eden asistanlara yönelik yapılan çevrimiçi bir anket platformu (Google Forms) aracılığıyla toplanan veriler ile yapılmıştır. Çalışmada dört grup (Grup 1: Ağız, diş ve çene cerrahisi asistanı; Grup 2: Periodontoloji asistanı; Grup 3: Ağız, diş ve çene cerrahisi uzmanı veya doktoru; Grup 4: Periodontoloji uzmanı veya doktoru) kullanılmış ve anketler her grupta 20'şer kişi olmak üzere 80 kişiye doldurtulmuştur. Doldurulan anketler; bireylerin yaş, cinsiyet, eğitim düzeyi, çalışma süresi, eğitim alma durumu gibi demografik bilgiler ile atık bilgi düzeyini ölçen soruları (50 soru) içermekteydi. Son üç aydan daha az kliniklerde çalışmış olan bireyler çalışmaya dâhil edilmemiştir. Çalışma için Tekirdağ Namık Kemal Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulundan onay alınmıştır (Karar tarih-no: 25.06.2024-2024.219.06.07). Araştırmanın tamamında araştırma ve yayın etiğine uyulmuştur. Araştırma anketleri katılımcılara 01.08.2024-31.08.2024 tarihleri arasında doldurtulmuştur.

Bilgi düzeyi değerlendirmeleri kişilerin anketlerde verdikleri doğru cevap sayısına göre belirlenmiştir (zayıf: 50 üzerinden 25'ten az doğru cevap, orta: 50 üzerinden 25-37 doğru cevap, iyi: 50 üzerinden 37'den fazla doğru cevap) (Cigerim ve Kaplan, 2020).

İstatistiksel analiz

Çalışmada bilgi düzeyi ana karakteristik olarak incelenmiştir. Daha önceki öğretim üyeleri ve asistanların incelendiği bir çalışmada bu gruplar için bilgi düzeylerinin standart sapmaları 3,58 ve 5,54 olarak tespit edilmiştir (Cigerim ve Kaplan, 2020). Bu sebeple standart sapma ortalaması (S) 4,56 olarak alınmıştır. %5 I. Tip hata ($\alpha = 0,05$) ve %95 güven düzeyinde yaklaşık %80 güç değeri için etki büyüklüğü (d, effect size) araştırmacılar tarafından 2 olarak kabul edilmiştir. Örneklem genişliği;

$n = Z^2 \times S^2) / d^2$ eşitliği kullanılarak hesaplanmıştır (Not: % 5 hata için Z değeri 1,96 dır).

Buna göre her grupta olması gereken kişi sayısı $n = (1,96^2 \times 4,56^2) / 2^2 = 20$ olarak tespit edilmiş ve 4 grupta toplam 80 kişinin anketleri değerlendirilmiştir. Çevrim içi anketlerin doğası gereği soru ve cevaplar belli olduğundan ve eksik cevap bulunduğunda anket verileri sisteme kaydolmadığından anketleri cevaplayan kişi sayısında kayıp olmamaktadır.

Üzerinde durulan özelliklerden sürekli değişkenler için tanımlayıcı istatistikler; ortalama, standart sapma, minimum ve maksimum değerler olarak ifade edilirken, kategorik değişkenler için sayı ve yüzde olarak ifade edilmiştir. Sürekli değişkenler bakımından Normallik testi Shapiro Wilk testi ile yapılmıştır. Sürekli değişkenler bakımından kategorik değişkenlere göre yapılacak ikiden fazla grup karşılaştırmalarında; Normallik sağlandığından Varyans Analizi testi kullanılmıştır. Diğer grup karşılaştırmalarında ise Student t testi kullanılmıştır. Hesaplamalarda istatistik önemlilik (anlamlılık) düzeyi %5 olarak alınmış ve hesaplamalar için SPSS (ver:21) istatistik paket programından yararlanılmıştır.

BULGULAR

Çalışmaya katılan 80 bireyin 32 (%40)'si erkek, 48 (%60)'i kadın; ortalama yaşı ise 31,21±5,71'dir. Tüm gruplar 20'şer kişiden oluşmuştur. Bireyler çalışma yıllarına göre değerlendirildiğinde 0-2 yıl, 3-4 yıl, 5-10 yıl, 11-15 yıl, 16 yıl ve fazla çalışanların oranları sırasıyla %36,25, %13,75, %38,75, %8,75 ve %2,50 idi. Bireyler çalıştıkları iş yerlerindeki tıbbi atık uygulamalarını %15 çok başarılı, %55 başarılı, %16,25 az başarılı, %1,25 başarısız bulmuşlar, %12,50 kişi ise fikir beyan etmemiştir (Tablo 1).

Tablo 1. Tanımlayıcı istatistikler

		Sayı (%)
Yaş (Yıl)	Ortalama±SS	31,21±5,71
	Medyan	29,50
	Min.-Maks.	24-51
Cinsiyet	Erkek	32 (40)
	Kadın	48 (60)
Unvan	Ağız, diş ve çene cerrahisi asistanı	20 (25)
	Periodontoloji asistanı	20 (25)
	Ağız, diş ve çene cerrahisi uzmanı veya doktoru	20 (25)
	Periodontoloji uzmanı veya doktoru	20 (25)
İş deneyimi (yıl)	0-2	29 (36,25)
	3-4	11 (13,75)
	5-10	31 (38,75)
	11-15	7 (8,75)
	16+	2 (2,50)
İş yerinizde atık uygulamaları başarılı mı?	Çok başarılı	12 (15,00)
	Başarılı	44 (55,00)
	Fikrim yok	10 (12,50)
	Az başarılı	13 (16,25)
	Başarısız	1 (1,25)

SS: Standart sapma, %: yüzde

Çalışmada incelenen grupların cevapları değerlendirildiğinde sırasıyla periodontoloji uzmanı veya doktoru (18 kişi), ağız diş ve çene cerrahisi asistanı (17 kişi), periodontoloji asistanı (17 kişi), Ağız, diş ve çene cerrahisi uzmanı veya doktoru (16 kişi) iyi düzeyde atık bilgisine sahipti. Hiçbir grupta zayıf düzeyde atık bilgisine sahip kişi yoktu (Tablo 2). Çalışmaya katılan bireylerin; cinsiyet, çalışma süresi, eğitim derecesi ve unvanlarına göre atık bilgi düzeylerinin değerlendirilmesinde anlamlı farklılık bulunmamıştır (Tablo 3).

Tablo 2. Grupların atık bilgi düzeyleri

Ağız ve diş sağlığı personeli	**Düzeylere Göre Kişi sayısı**		
	İyi	**Orta**	**Zayıf**
Ağız, diş ve çene cerrahisi asistanı	17	3	0
Periodontoloji asistanı	17	3	0
Ağız, diş ve çene cerrahisi uzmanı veya doktoru	16	4	0
Periodontoloji uzmanı veya doktoru	18	2	0

Zayıf: 50 soru üzerinden 25'ten az doğru cevap; orta: 50 üzerinden 25-37 doğru cevap; iyi: 50 üzerinden 37'den fazla doğru cevap

Tablo 3. Atık bilgi düzeyindeki toplam doğru cevap sayılarının cinsiyete, bireylerin çalışma yıllarına, eğitim derecesine ve pozisyona göre karşılaştırılması

		Kişi sayısı	**Atık Bilgi Düzeyi Ortalaması ±SS (n)**	**Min.-Maks. (n)**	**Medyan (n)**	**p**
Cinsiyet	Erkek	32	41,41±3,79	34-47	41,50	0,526
	Kadın	48	41,94±3,56	34-49	42,00	
Çalışma yılı	0-2	29	41,17±3,48	34-47	42,00	0,293
	3-4	11	42,45±3,45	36-47	43,00	
	5-10	31	41,65±3,85	34-49	41,00	
	11-15	7	44,00±2,24	40-46	45,00	
	16+	2	39,00±7,07	34-44	39,00	
Eğitim derecesi	Doktora	33	41,70±4,02	34-47	42,00	0,954
	Uzmanlık	47	41,74±3,40	35-49	42,00	
Unvan	Ağız, diş ve çene cerrahisi asistanı	20	41,55±3,94	34-47	42,00	0,617
	Periodontoloji asistanı	20	41,50±3,03	36-47	42,00	
	Ağız, diş ve çene cerrahisi uzmanı veya doktoru	20	41,20±4,12	34-47	41,00	
	Periodontoloji uzmanı veya doktoru	20	42,65±3,48	36-49	43,50	

SS: Standart sapma, n: doğru cevap sayı

TARTIŞMA

Zararlı atıkların bertaraf edilmesi, genel atıkların tehlikeli atıklardan ayrılması ve atıkların azaltılması ile güvenli atık yönetimi yapılabilir. Bu da ancak iyi bir atık bilgi düzeyi ile sağlanabilir. Tüm sağlık çalışanları, atık yönetimini, mezun olmadan öğrenmeleri gerektiği gibi aynı zamanda mezuniyet sonrası eğitimler ile de bilgilerini güncellemelidir (Soliman ve Ahmed, 2007; Sharma ve ark., 2013; Cigerim ve Kaplan, 2020).

Çalışma; üniversite veya özel ağız ve diş sağlığı merkezi/hastanesi kliniklerinde periodontoloji ve ağız, diş ve çene cerrahisi bölümlerinde çalışan uzman/doktoralı diş hekimleri ile üniversitelerde öğrenim gören periodontoloji ve çene cerrahisi uzmanlık veya doktora eğitimlerine devam eden asistanlara yönelik yapılan çevrimiçi bir anket platformu (Google Forms) aracılığıyla toplanan veriler ile yapılmıştır (Monica ve ark., 2022). Çevrim içi veri toplama sayesinde; kağıtlardaki anketlerin bilgisayara aktarılması sırasında oluşabilecek insan hatası ile yüz yüze veri toplama esnasında iken verilen cevaplarda yanlış yapma korkusu veya sorulan sorulara eksik cevap verme gibi olası problemler ile karşılaşılmamaktadır (Subramanian ve ark., 2020). Bu sebeple bu çalışmada çevrim içi veri toplama yöntemi kullanılmıştır.

Sharma ve ark., 10 soruya 4'ten az yanıt verilmesi durumunda atık konusundaki bilgi düzeyini zayıf olarak değerlendirmişlerdir. Meslekleri incelemeleri doğrultusunda; yaklaşık olarak diş hekimlerinin %25'inin, hemşirelerin %36'sının, laboratuvar teknisyenlerinin %40'ının ve temizlikçiler ile bakım personelinin ise %45'inin kötü seviyede olduğunu belirlemişlerdir (Sharma ve ark., 2013). Atık bilgi düzeyi değerlendirmesinin kişilerin anketlerde verdikleri doğru cevap sayısına göre belirlendiği bu çalışmada (zayıf: 50 üzerinden 25'ten az doğru cevap, orta: 50 üzerinden 25-37 doğru cevap, iyi: 50 üzerinden 37'den fazla doğru cevap) incelen grupların cevapları değerlendirildiğinde periodontoloji uzmanı veya doktoru (18 kişi), ağız diş ve çene cerrahisi asistanı (17 kişi), periodontoloji asistanı (17 kişi), ağız diş ve çene cerrahisi uzmanı veya doktoru (16 kişi) iyi düzeyde atık bilgisine sahipti. Hiçbir grupta zayıf düzeyde atık bilgisine sahip kişi yoktu. Bu çalışmadaki sonuçlara göre çalışma gruplarındaki kişilerin atık bilgi düzeyleri iyi de olsa bilgilerini güncellemeleri için hayat boyu eğitim almaları gerekir.

Bu çalışmada, çalışma yılı ile atık bilgi düzeyi arasındaki ilişki incelendiğinde, çalışma yılının tıbbi atık bilgi düzeyi üzerinde etkili olmadığı görülmüş olup, bu sonuç Hasçuhadar ve ark., ile Koseoglu ve ark., tarafından yapılan çalışmalarla tutarlıdır (Hasçuhadar ve ark, 2007; Koseoglu ve ark., 2019). Çalışmaya katılan bireylerin; çalışma süresine göre 11-15 sene aralığında çalışanların 50 soru üzerinden ortalama 44 doğru cevap şeklinde olup diğerlerinden daha fazla olması dikkat çekicidir ve bu durum Cigerim ve Kaplan tarafından yapılan bir anket çalışmasındaki bulgularla benzerlik göstermektedir (Cigerim ve Kaplan, 2020).

Cigerim ve Kaplan ile Koseoglu ve ark. çalışmalarında olduğu gibi bu çalışmada da atık bilgi düzeyi ile cinsiyetler arasında anlamlı farklılık bulunmamıştır (Koseoglu ve ark., 2019; Cigerim ve Kaplan, 2020).

Anket yöntemleri hızlı, ucuz ve geçerli yöntemler olmalarına rağmen bu çalışmanın limitasyonu anket cevap şıklarının varlığının doğru cevaplar için hatırlatıcı rol oynayabilmeleridir (Gilbert ve ark., 2002; Charani ve ark., 2011).

Sonuç olarak, uzman/doktoralı diş hekimleri ya da bu eğitimleri alan diş hekimlerinin atık bilgi düzeylerinin en üst seviyede olması beklenir. Bu sayede birlikte çalıştıkları personelin de bilgi atık düzeyi iyi düzeye ulaşabilir. Bu çalışmada görüldüğü üzere gruplardaki kişilerin hiçbiri zayıf atık bilgi düzeyine sahip olmadığı gibi en üst seviyede atık bilgi düzeyine de (%85) hepsi sahip değillerdi. Bu sebeple hangi branş olursa olsun tüm diş hekimleri zaman zaman atıklar konusunda bilgilerini güncellemelidir.

Teşekkür: Bu çalışmanın istatistiksel analizi Duygu KORKMAZ YALÇIN (Van Yüzüncü Yıl Üniversitesi, Tıp Fakültesi, Biyoistatistik A.D.) tarafından yapılmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan eder.

Etik Onay: Bu araştırmanın etik kurul onayı 25.06.2024 tarihli, 2024.219.06.07 sayılı karar no ile Tekirdağ Namık Kemal Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan alınmıştır.

Yazar Katkısı: Tüm yazarlar çalışmanın dizaynında görev yapmıştır. Anket soruları T.D. ve V.K. tarafından hazırlanmış, T.D. tarafından katılımcılara gönderilmiştir. Verilerin analizleri V.K. ve T.D. tarafından yapılmıştır. Makalenin yazımında tüm yazarlar görev almıştır ve makalenin son halini okumuş ve onaylamıştır.

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Effects of Acupressure Application on Blood Pressure and Disease-Related Symptoms in Individuals with Hypertension: An Experimental Study

Akupresur Uygulamasının Hipertansiyonu Olan Bireylerde Kan Basıncı ve Hastalığa Bağlı Semptomlara Etkisi: Deneysel Bir Çalışma

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ABSTRACT

Objective: Taking symptoms under control is important to calm the individual with hypertension and reduce complications. This study aimed to determine the effects of acupressure on blood pressure, fatigue, insomnia and headache in patients with hypertension.

Material and Method: The research was an experimental study. Research data were collected between August 2017 and July 2018. The research sample consisted of acupressure intervention groups and a control group with 40 patients in each group for a total of 80 patients. Acupressure applied to their intervention groups for a total of seven sessions of 20 min each over one week, once a day on seven days a week. Data was collected by means of a personal information form, fatigue severity scale, numeric pain scale and Pittsburgh sleep quality index.

Results: In comparison with the control group, a significant reduction was seen over time in the levels of blood pressure, fatigue, headache and insomnia in the acupressure intervention groups ($p<0.05$).

Conclusion: Acupressure interventions were found to effective in reducing levels of blood pressure, fatigue, insomnia and headache. It was seen that in addition to their use in routine nursing care acupressure treatments can be accepted as effective nursing interventions that reduce blood pressure, fatigue, insomnia and headache of patients with hypertension.

Keywords: *Acupressure, Blood pressure, Fatigue, Insomnia, Head pain, Hypertension*

ÖZET

Giriş: Semptomları kontrol altına almak hipertansiyonlu bireyi sakinleştirmek ve komplikasyonları azaltmak için önemlidir. Bu çalışma hipertansiyonlu hastalarda akupresürün kan basıncı, yorgunluk, uykusuzluk ve baş ağrısı üzerindeki etkilerini belirlemeyi amaçlamıştır.

Materyal ve Metot: Araştırma deneysel bir çalışmadır. Araştırma verileri Ağustos 2017 ile Temmuz 2018 arasında toplanmıştır. Araştırma örneklemi akupresür müdahale grupları ve her grupta 40 hasta olmak üzere toplam 80 hastadan oluşan bir kontrol grubundan oluşmuştur. Müdahale gruplarına akupresür, haftada yedi gün, günde bir kez olmak üzere bir hafta boyunca her biri 20 dakikalık toplam yedi seans uygulanmıştır. Veriler kişisel bilgi formu, yorgunluk şiddet ölçeği, sayısal ağrı ölçeği ve Pittsburgh uyku kalitesi indeksi aracılığıyla toplanmıştır.

Bulgular: Kontrol grubuyla karşılaştırıldığında, akupresür müdahale gruplarında kan basıncı, yorgunluk, baş ağrısı ve uykusuzluk seviyelerinde zamanla anlamlı bir azalma görülmüştür ($p<0,05$).

Sonuç: Akupresür müdahalelerinin kan basıncı, yorgunluk, uykusuzluk ve baş ağrısı seviyelerini azaltmada etkili olduğu bulundu. Rutin hemşirelik bakımında kullanılmasına ek olarak akupresür tedavilerinin hipertansiyonlu hastaların kan basıncını, yorgunluğunu, uykusuzluğunu ve baş ağrısını azaltan etkili hemşirelik müdahaleleri olarak kabul edilebileceği görüldü.

Anahtar kelimeler: *Akupresür, Kan basıncı, Yorgunluk, Uykusuzluk, Baş ağrısı, Hipertansiyon*

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INTRODUCTION

Hypertension is an established risk factor for chronic diseases and has also become a cause of death globally (Gao et al., 2024). Hypertension is drawing serious threat to human health. American Heart Association is emphasized that, hypertension is defined as either a systolic blood pressure measurement everlastingly higher than 129 mmHg or a diastolic blood pressure higher than 89 mmHg (Satapathy et al., 2022).

Patients with hypertension experience a large number of symptoms such as exhaustion, fatigue, headache, tachycardia, dyspnea, ringing in the ears, nasal bleeding, swelling of the legs and insomnia (Mendoza et al., 2022). These symptoms which generally have a negative influence on the patients' quality of life have been shown to be associated with each other (McGrath et al., 2017).

Today, pharmacological and non-pharmacological methods are used in symptom management for hypertension patients (Albulushi et al., 2024). Using antihypertensive drugs is the first line of treatment. Also, traditional Chinese medicine have achieved curative effects in the treatment of hypertension (Zhang et al., 2019). Non pharmacologic therapies are vital in managing symptoms. The pharmacological drugs effects of detrimental are excessive. Therefore, patients prefer nonpharmacological therapies rather than medication. Among these therapies such as aromatherapy, reiki, massage, acupuncture, acupressure and music (Yeni et al., 2022).

Acupressure, which is among non-pharmacological therapies, is one of the ancient healing methods. This method enables the proper functioning of energy channels through applying pressure to acupuncture points with fingers, tennis balls or special stimulation devices in order to activate the power of the body to heal itself, to regulate energy flow and to remove uncomfortable symptoms. Because acupressure and acupuncture have the same working mechanism, the effect is the same (Cha and Park, 2020). Acupressure is a non-invasive, safe, effective and side-effect free method. Its basic feature is to treat the disease by using the organism's own means and removing the symptoms without getting any material to the organism from the outside. Stimulating a few different points effective in the same disease simultaneously can remove a large number of symptoms (Hmwe et al., 2020). Acupressure is used frequently by nurses as a clinical and comprehensive nursing intervention (Khanghah et al., 2019). It is stated that it should be included in care plans of nurses, especially due to being a complementary-alternative method in symptom control (Mai et al., 2022).

In recent years, the use of acupressure in the management of symptoms has increased worldwide. Acupressure has been found to relieve symptoms in patients with hypertension and for therapeutical purposes by showing a regulating effect on blood pressure (Kim et al., 2013; Yeh et al., 2015; Lin et al., 2016).

Some randomized controlled studies show that acupressure decrease both systolic and diastolic blood pressure, removing headache, fatigue, sleep problems (Kim et al., 2013; Simoncini et al., 2015; Yeh et al., 2015; Wang et al., 2017; Waits et al., 2018; Sokunbi et al., 2020; Lu et al., 2022; Chang et al., 2024).

When the literature is reviewed, although there are a great number of studies which have examined the effects of acupressure in different disease groups, no studies have been found in our country about acupressure in hypertension patients (Zeng et al., 2016; Waits et al., 2018; Sokunbi et al., 2020; Turkmen and Turfan, 2020; Alinaghizadeh et al., 2021; Kucukkelepce et al., 2021; Korelo et al., 2022; Mai et al., 2022; Lu et al., 2022; Chang et al., 2024).

The aim of the present study was to determine the effects of acupressure on blood pressure, fatigue, insomnia and headache in patients with hypertension.

Hypotheses 1. Acupressure interventions have an effect on blood pressure, fatigue, insomnia and headache fatigue level of patients with hypertension.

Hypothesis 0. Acupressure interventions have no effect on blood pressure, fatigue, insomnia and headache fatigue level of patients with hypertension.

MATERIAL and METHOD

Study Design and Participants

The study was conducted as an experimental study with repetitive measurement, randomized design and experimental and control group.

The population consisted of 450 patients diagnosed with hypertension who referred to cardiology polyclinic of a university hospital. The patients who did not meet the research criteria were excluded, 280 were left. 170 of these patients refused to participate in the study were excluded from the list. Of 110 patients, 30 refused to participate. The study was completed with the remaining 80 patients. The sample size was appropriate as 40 patients in each group with a calculation based on 80% statistical power, 0.10 effect size and 0.05 margin of error. The study was conducted with 40 in the experimental group and 40 in the control group, who met the inclusion criteria and agreed to participate in the study.

Hypertension patients who met the following conditions were included in the study: Hypertension patients who met the following conditions were included in the study: (1) a diagnosis of hypertension; (2) uses antihypertensive; (3) 18 years of age or older; (4) no communication problem; (5) a status of 5 or more on the Pittsburgh sleep quality index total score of 5 and higher; (6) a status of 27 or more on the fatigue severity index total score of 5 and higher; (7) a score of 4 or more on the numerical pain scale; (8) no burns, scars, cuts or scratches, or deformities in

the area where acupressure would be applied; (9) have not had acupressure previously; (10) conscious; (12) no psychological illness; and (13) agreed to participate in the research.

Ethical Approval

Ethical approval was obtained from an ethics committee within the scope of the study (Date: 08.08.2017, Ethics committee no: 2017-8/4).

Data Collection Tools

Personal information form, fatigue severity index, numerical pain scale, Pittsburgh sleep quality and blood pressure follow-up form index were used for data collection.

Personal Information Form

This form includes questions to find out descriptive and disease related characteristics of the patients.

Fatigue Severity Index

This scale was developed by Krupp et al. Each question is graded between 1 and 7 (Simoncini et al., 2015). While the total score differs between 9 and 63, a total score of 27 and higher shows that there is fatigue. An increase in total score means increase in fatigue severity. The higher the total score is the higher fatigue is. Individuals are asked to tell the options which fit them by considering their states within the past week. Fatigue severity index has shown acceptable internal consistency, validity and sensitivity to clinical changes. The Turkish validity and reliability of the scale was confirmed in a study by Armutlu et al. They found the Cronbach Alpha internal consistency coefficient of the scale as 0.89 (Armutlu et al., 2017). Cronbach Alpha was for this study as 0.809.

Numerical Pain Scale

This method used in finding out pain severity aims to make the patient explain pain with numbers. It is frequently used in clinic due to being easy to apply. Numerical pain scale includes numbers gradually increasing placed on a line with specific intervals. In the scale, absence of pain starts with (0) and reaches the level of unbearable pain (10) (Aslan,2002).

Pittsburgh Sleep Quality Index

PSQI was developed by Buysse et al. It is a scale which gives information about sleep quality and sleep problems within the past month and it can be used easily and commonly both for clinic and research purposes (Buysse et al., 1989). While 19 of the 24 questions of the scale are answered by the individual, 5 questions are answered by the individual's friend, if there is. The last 5 questions are not included in the scoring. Only the 19 questions answered by the individual are taken into consideration in the assessment. Each item in the scale is scored as 0 (no problem) -3 (serious problem). Total scores of the seven sub-dimensions differ between 0 and 21 and give the total PSQI score. Agargun conducted the Turkish validity and reliability study of the scale in our country (Agargun et al., 1996). Cronbach alpha value of the Turkish validity and reliability study is 0.80, for this study, cronbach alpha was found as 0.802.

Blood Pressure Follow-Up Form

This form, which was created by the researchers, records the total weekly blood pressure and as well as the times of measurement.

Procedures

During the study, the routine treatment of the patients in all two groups was continued. In support of their routine treatment, a total of seven sessions of acupressure were conducted with the patients of the intervention (Acupressure) group, with seven sessions a week, once a day, over one week. Each session lasted 20 min. All sessions were held by the same researcher (G.A.). However, no intervention was made to the control group. The researcher took part in 16 h of Acupressure training, four hours a day for four days. Previous studies in the literature were examined, and an acupressure intervention protocol was prepared in line with the views of an expert (Zeng et al., 2016; Wang et al., 2017; Alinaghizadeh et al., 2021).

At the first meeting, information was given to the patients regarding the aim of the research. Participants were given 15 minute to decide whether to participate in this study. The researchers obtained written approval from the patients. Patients who agreed to participate in the research were assigned to an intervention group (Acupressure) or the control group. The patients who came to the polyclinic on the same days of the week were taken in the same group. The patient description form was completed by the researchers.

Intervention

Acupressure Group

The researcher (GA) applied acupressure. In order to contact information was taken by the researcher. Groups of 4-5 were formed for the acupressure application. The groups were arranged according to the patients were available. The groups were arranged Monday-Sunday and Tuesday-Monday. 8 patients stopped acupressure application. 8 new patients were taken again to complete the sample group.

The first acupressure intervention was conducted in a predetermined room in the hospital after conditions not disturbing the patients (sound, light…) were met. The other sessions were made in the patients' homes. Home addresses of the participants selected for this study were obtained from the hospital records. Before each acupressure application session, the patients' blood pressures were measured and recorded. The major acupoints for this study was Ht7- Shenmen (insomnia), LI4- Hegu (headache) and St36-Zusanli (fatigue). The protocol of acupressure was prepared with the expert was prepared with the expert (as shown in the steps of acupressure). Acupressure applied to their intervention groups for a total of

seven sessions of 20 min each over one week, once a day on seven days a week. Acu points receiving the intervention were as follows Fig. 1.

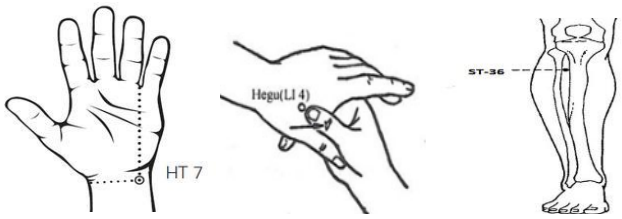

Figure. 1. Acupressure application points.

Steps of Application Acupressure

1.Wash hands before application.

2. The patient is given suitable position.

3. Before applying direct pressure on each point, preparative taps are made to each point for about 10 seconds in order to loosen the point area, to relax the soft tissue and to decrease tension by increasing local blood build up.

4. Pressure are applied by the researcher for 2 minutes.

5. Symmetrically, pressure is applied to each acupressure point.

6. While applying pressure, care are taken for the individual's sensitivity (threshold of pain) not to create tissue damage.

7. The repetitive pressures on each point are made with a frequency which did not disturb the individual and did not cause pain.

8. All applications are made every day at the same period of time.

9. 10 minutes after acupressure intervention ended, the patients' blood pressures are measured again and recorded.

10. The hands are washed and the application is recorded.

Control Group

In the control group patients, no intervention was made expect for their routine treatment during the study. While their pre-test data were being taken at the first meeting, the patients were explained that he same practices would be conducted in the hospital or in their home on day 7. 7 days later, their post-test data (PIF, FSI, NPS and PSQI) were collected and their blood pressures were measured and recorded. The Fig. 2. depicts the research plan.

RESEARCH PLAN Determination of patients who meet the research criteria Sample of the study (n=80)	
ACUPRESSURE GROUP (n=40)	**CONTROL GROUP (n=40)**
Pre-Test - Informing patients about the study and obtaining informed consent - PIF - FSI - NPS - PSQI	**Pre-Test** - Informing patients about the study and obtaining informed consent - PIF - FSI - NPS - PSQI
Acupressure Application Total of seven sessions.	No acupressure.
Post-Test (At the end of session seven) - FSI - NPS - PSQI	**Post-Test (At the end of session seven)** - FSI - NPS - PSQI

Figure. 2. Research plan.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 statistical software (IBM, Armonk, New York, USA). The data obtained are presented as arithmetic mean, standard deviation, number, percentage, minimum-maximum value. As well as $\chi 2$ analysis for the comparison of the 2 groups' demographic characteristics (categorical measurements), independent-group t test and Mann-Whitney U test for the comparison of the groups' systolic blood pressure, diastolic blood pressure, fatigue severity index, numerical pain scale and pittsburgh sleep quality index scores, dependent-groups variance analysis and Will Coxon test for inter group comparisons, and Cronbach's α coefficients for internal consistency.

RESULTS

Variables of the patients in the experimental group and control group were compared in Table 1. Except for the rates of cigarette use ($p=0.01$) control variables of the patients in the experimental and the control group are similar to each other ($p>0.05$).

Table 1. Comparison of descriptive characteristics of groups

		Experimental		Control		Significance
		n	%	**n**	%	
Gender	Female	23	57.5	18	45.0	x^2=1.251, p=0.263
	Male	17	42.5	22	55.0	
Educational level	Literate	7	17.5	5	12.5	x^2=4.511, p=0.341
	Illiterate	19	47.5	15	37.5	
	Primary	12	30.0	13	32.5	
	Secondary	2	5.0	4	10.0	
	High school	-	-	3	7.5	
Marital status	Single (Single or divorced…)	4	10.0	1	2.5	p=0.359*
	Married	36	90.0	39	97.5	
Profession	Officer/Worker	2	5.0	1	2.5	x^2=7.019, p=0.135
	Retired	5	12.5	9	22.5	
	Housewife	23	57.5	18	45.0	
	Unemployed	8	20.0	4	10.0	
	Other	2	5.0	8	20.0	
Cigarette	Yes	2	5.0	11	27.5	x^2=8.367, p=**0.015**
	No	29	72.5	19	47.5	
	Quit	9	22.5	10	25.0	
Alcohol	No	40	100	39	97.5	p=1.000*
	Quit	-		1	2.5	
Duration of illness	6-12 months	1	2.5	2	5.0	x^2=0.377, p=0.945
	1-5 years	12	30.0	11	27.5	
	6-9 years	16	40.0	16	40.0	
	≥10 years	11	27.5	11	27.5	
Regular drug use	Yes	36	90.0	38	95.0	p=0.675*
	No	4	10.0	2	5.0	
Frequency of having BP measured	Every day	2	5.0	5	12.5	x^2=4.161, p=0.125
	One in a while	25	62.5	29	72.5	
	Never	13	32.5	6	15.0	
		$\bar{X}$± SD		**$\bar{X}$± SD**		
Age (years)		60.43± 11.47		57.13± 9.78		t=1.385, p=0.170

*p<0.05; *Fisher's exact Chi-square test; *Mann Whitney- U test; HT: hypertension; BP: blood pressure.

In Table 2, pre-acupressure fatigue, insomnia, pain scales were found to be higher in the experimental scores and blood pressures of the patients in the two groups were compared, DBP, NPS and PSQI average group (p=0.031, p=0.002, p=0.000).

Table 2. Comparison of pre-intervention values of patients in the experimental and control group between groups

	n	**Acupressure group (n=40)**			**Control group (n=40)**			
		Min.	**Max.**	**$\bar{X}$± SD**	**Min.**	**Max.**	**$\bar{X}$± SD**	**Test & p***
SBP	40	130	200	152.00± 18.84	130	170	144.88± 12.48	U=643.500, p=0.124
DBP	40	70	180	95.75± 17.23	70	110	88.38± 10.88	U=585.000 **p=0.031**
FSI	40	38.00	63.00	55.55±5.99	30.00	63.00	54.83± 6.79	U=756.500 p=0.675
NPS	40	4.00	9.00	6.60±1.19	4.00	8.00	5.80± 1.02	t=3.225 p=**0.002**
PSQI	40	7.00	18.00	13.35±2.38	8.00	14.00	11.28± 1.81	t=4.387 p=**0.000**

*p<0.05; *Mann Whitney- U test, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, FSI: fatigue severity index, NPS: numerical pain scale, PSQI: Pittsburgh sleep quality index, SD: standard deviation.

When the intragroup SBP and DBP values of two groups were compared in Table 3; the difference between pre and post-acupressure SBP and DBP of the patients in two groups was found to be statistically significant ($p<0.05$ for each). It was found that post-test blood pressure values of the experimental group decreased in all measurements, while post-test blood pressure values of the control group patients were found to increase (Table 3).

Table 3. Comparison of pre and post-test values of patients

Groups		Measurement	Pre-test	Post-test	Test & p*
			$\bar{X}$± SD	$\bar{X}$± SD	
Acupressure group	SBP	First	152.00± 18.84	143.75± 16.44	t=6.983, p=**0.000**
		Second	150.75± 13.47	142.75± 11.54	t=4.853, p=**0.000**
		Third	151.50± 15.94	143.50± 14.06	t=5.551, p=**0.000**
		Fourth	146.25± 11.92	139.25± 8.88	t=6.121, p=**0.000**
		Fifth	148.75± 14.36	141.88± 10.72	t=5.394, p=**0.000**
		Sixth	145.50± 10.85	141.75± 10.10	t=2.644, p=**0.012**
		Seventh	146.00± 12.57	141.75± 9.03	Z=-2.769, p=**0.005**
	DBP	First	95.75± 17.23	86.88± 14.88	t=7.047, p=**0.000**
		Second	90.50± 8.46	84.75± 10.62	t=3.433, p=**0.001**
		Third	92.25± 8.77	86.38± 8.62	t=4.693, p=**0.000**
		Fourth	87.88± 6.49	83.25± 7.97	t=4.116, p=**0.000**
		Fifth	90.00± 7.76	82.88± 10.18	t=6.007, p=**0.000**
		Sixth	90.00± 7.16	82.13± 7.06	t=6.565, p=**0.000**
		Seventh	88.75± 8.22	81.75± 8.66	t=6.048, p=**0.000**
Control group	SBP	First	144.88± 12.48	148.75± 13.06	t=4.244, p=**0.000**
	DBP	Second	88.38± 10.88	93.00± 9.79	Z=-2.143, p=**0.032**

*p<0.05; *Z = Will Coxon Test; SBP: systolic blood pressure, DBP: diastolic blood pressure, SD: standard deviation

Intragroup comparisons of FSI, NPS and PSQI pre and post-test score averages of the patients in the experimental and control group and intergroup of post-test score averages are shown in Table 4.

Statistically significant difference was found between the FSI pre-test (55.55± 5.99; p=0.610) and FSI post-test score averages (45.93± 4.27; p=0.000); NPS pre-test (6.60± 1.19; p=0.000) and post-test score averages (4.25± 1.28; p=0.000) and PSQI pre-test (13.35± 2.38; p=0.000) and post-test score averages (7.80± 2.02; p=0.000) of the patients in the experimental groups (p=0.000). The difference between NPS pre-test (5.80± 1.02) and post-test score averages (6.45± 1.54) of the control group was found to be statistically significant (p<0.05; Table 4). Also it was determined that the NPS post-test mean score increased.

When the post-test score values were compared between the two groups, SBP post-test score average of the experimental group (141.75± 9.03) was found to be lower than control group post-test SBP score average (148.75±13.06) (p>0.05 for each). Experimental group DBP post-test score average (81.75± 8.66) was found to be less than control group post-test DBP score average (93.00± 9.79) (p=0.032). There was a significant difference between post-test FSI score average of the experimental (45.93± 4.27) and control group (55.58± 4.84) (p=0.000 and p=0.610) and control group fatigue score averages were higher. A significant difference was also found between NPS score averages of the experimental (4.25± 1.28) and control groups (6.45± 1.54) was found to be statistically significant (p=0.000 and p=0.037). Pain score averages of the control group were higher. Post-test PSQI total score averages of the experimental group (7.80± 2.02) were less than of the control group (10.95± 2.76) (p=0.000 and p=0.537; Table 4).

Table 4. Intragroup and intergroup comparison of scores of the patients

		Pre test	Post test	Test & p*
		$\bar{X}$± SD	$\bar{X}$± SD	
SBP	**Acupressure group**	152.00± 18.84	141.75± 9.03	
	Control group	144.88± 12.48	148.75± 13.06	t=4.244 p=**0.000**
	Test & p*		t=-2.791 p=**0.007**	
DBP	**Acupressure group**	95.75± 17.23	81.75± 8.66	
	Control group	88.38± 10.88	93.00± 9.79	Z=-2.143 p=**0.032**
	Test & p*		U=329.000 p=**0.000**	
FSI	**Acupressure group**	55.55± 5.99	45.93± 4.27	t=14.213 p=**0.000**
	Control group	54.83± 6.79	55.58± 4.84	Z=-0.510 p=0.610
	Test & p*		U=120.000 p=**0.000**	
NPS	**Acupressure group**	6.60± 1.19	4.25± 1.28	t=17.206 p=**0.000**
	Control group	5.80± 1.02	6.45± 1.54	t=-2.161 p=**0.037**
	Test & p*		t=-6,970 p=**0.000**	
PSQI	**Acupressure group**	13.35± 2.38	7.80± 2.02	t=13.703 p=**0.000**
	Control group	11.28± 1.81	10.95± 2.76	t=0.623 p=0.537
	Test & p*		t=-5.824 p=**0.000**	

*p<0.05; *Z = Will Coxon Test; SBP: systolic blood pressure, DBP: diastolic blood pressure, FSI: fatigue severity index, NPS: numerical pain scale, PSQI: Pittsburgh sleep quality index, SD: standard deviation.

DISCUSSION

In this section, the results of the present study, which was conducted to find out the effects of acupressure application on hypertension patients' blood pressures, fatigue, insomnia and headache symptoms, were discussed. Both SBP and DBP were found to decrease after each acupressure session in the experimental group when compared to the initial SBP and DBP results.

SBP and DBP post test results of the patients in the experimental group were found to be lower when compared with the patients in the other group. These results confirm hypothesis 1. In their randomized controlled studies, they concluded that acupressure decreased both systolic and diastolic blood pressure in hypertensive patients and that further studies were needed to assert that using it as a subsidiary care to antihypertensive treatment for this patient group could be useful in increasing quality of life and to determine the suitable acupressure application time (Kim et al., 2013; Yeh et al., 2015; Lin et al., 2016;). The results of different studies conducted on stroke patients and patients receiving invasive mechanical ventilation support have also concluded that acupressure is effective in decreasing blood pressure (Cingolani et al., 2019).

Fatigue levels of the experimental group were found to decrease following acupressure application. Fatigue levels of the patients in the experimental group were found to be less than those of the patients in the control group. These results support the research hypothesis 1. Studies about the effects of acupressure on fatigue have also reported that fatigue symptom decreased significantly with this practice (Kim et al., 2013; Simoncini et al., 2015; Yeh et al., 2015; Lin et al., 2016; Wang et al., 2017; Waits et al., 2018; Sokunbi et al., 2020; Korelo et al., 2022; Lu et al., 2022; Mai et al., 2022;). A meta-analysis study conducted in 2024 also stated that acupressure was effective in relieving patients' fatigue levels, similar to our findings (Chang et al., 2024). In a randomized controlled study conducted it was reported that acupressure had positive effects in removing fatigue (Çeçen and Lafcı, 2021). We can say that acupressure is effective in alleviating fatigue in patients receiving hypertension, particularly when the Shenmen acupoint is used together with other acupoints and is effective without the application of special equipment.

It was seen that the patients in the experimental group had less headaches, and they had very low headache scores when compared with patients in the control group. The outcomes of present study confirm the

research hypothesis 1. In a study, it was reported that acupressure is an effective method for headaches (Lu et al., 2022). In other studies, it has been supported that acupressure is effective in decreasing pain in cancer patients, and pain due to acute skeletal muscle injury, labor pain resulting from neck and shoulder nerve destruction, pain due to intramuscular injection and back aches (; Tan et al., 2021; Dragomon et al., 2022; Mai et al., 2022; Behkam,2024).

It was seen that the patients in the experimental group had decreased insomnia problems and experienced less insomnia than patients in the control group following acupressure application. These results confirm hypothesis 1. No studies were found about the effects of acupressure on hypertension patients in the literature review. For this reason, the results of the study were discussed with the results of studies on different patient groups. In literature, it has been reported that acupressure decreases insomnia significantly (Waits et al., 2018; Yeung et al., 2022). In addition, in the randomized controlled studies they conducted that acupressure was effective in solving sleep problem (Wang et al., 2017; Sokunbi et al., 2020). In addition, it has also been found that acupressure increases sleep quality in Alzheimer patients and patients with renal disease (Simoncini et al., 2015). Similar results were obtained in a study conducted in Indonesia in 2024. The study was conducted that acupressure release neurotransmitters such as serotonin and activate the opioid system. Therefore, by producing body relaxation, it can improve sleep quality. The massage points, especially on the shoulder, neck, or head area itself can produce varying degrees of body relaxation and thus result in a better quality of sleep. In addition, this can be due to the mental effects and emotional effects of massage (Yuniarsih et al., 2024). This studies have mentioned that further studies are required to find out whether the same effect exists for different patient groups.

The research is limited to the patients who received cardiology polyclinic, and the results of this study cannot be generalized to patients outside the study group.

Conclusion

In study, it was shown that acupressure is effective in decreasing both systolic and diastolic blood pressure, fatigue, insomnia and headache of hypertension patients. For this reason, it is recommended for health professionals to be encouraged to use acupressure with pharmacological methods in order to decrease symptoms such as fatigue, headache and insomnia which have a negative influence on hypertension patients' blood pressure and the patients' quality of life.

It was found that integrative methods of symptom management should be routinely integrated into nursing practice. Acupressure is the one of integrative methods and simple to use and inexpensive. Also, acupressure is non-invasive applications so it can also be incorporated in nursing care. When nurses use acupressure, it will help improve the quality of nursing care. Future studies with larger sample sizes are recommended to generalize the findings.

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Author contributions

Conceptualization GA, EYK; Data curation GA, Formal analysis GA, EYK; Methodology GA,EYK; Software GA; Supervision EYK; Validation GA, EYK; Visualization GA,EYK; Roles/Writing - original draft GA; Writing - review and editing EYK

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Association of Vitamin D and Magnesium Deficiencies with Clinical Outcomes in Sepsis

D Vitamini ve Magnezyum Eksiliklerinin Sepsisde Klinik Sonuçlarla İlişkisi

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ABSTRACT

Objective: This study aims to investigate the association of vitamin D and magnesium levels with the severity of sepsis and septic shock in intensive care unit patients.

Material and Method: A retrospective study was conducted in the ICU of a tertiary hospital, involving 299 sepsis patients admitted between January 2017 and January 2019. Patients' demographic data, vitamin D and magnesium levels, labarotory parameters, and clinical scores (APACHE II, SOFA, SAPS II) were collected at admission and discharge. Statistical analyses, including chi-square and correlation analysis, were performed to evaluate the association between these micronutrients and mortality.

Results: The results showed that while hypomagnesemia was associated with higher clinical severity scores, including APACHE II and SOFA ($p<0.05$), neither vitamin D nor magnesium levels were independently predictive of mortality. Magnesium deficiency correlated with worse clinical outcomes, ($p<0.05$) but its association with mortality remained inconclusive ($p>0.05$). Similarly, low vitamin D levels, though prevalent, did not significantly influence survival ($p>0.05$).

Conclusion: Vitamin D and magnesium levels were not independently associated with mortality in sepsis patients. However, magnesium deficiency was linked to higher severity scores, indicating its potential role in disease progression. Further research is needed to explore the therapeutic implications of correcting these deficiencies in critically ill patients.

Keywords: *Sepsis, Vitamin D, Magnesium, APACHE II, SOFA*

ÖZET

Giriş: Bu çalışmanın amacı yoğun bakım hastalarında D vitamini ve magnezyum düzeylerinin sepsis ve septik şokun şiddeti ile ilişkisini araştırmaktır.

Materyal ve Metot: Üçüncü basamak bir hastanenin YBÜ'sünde Ocak 2017 ile Ocak 2019 tarihleri arasında kabul edilen 299 sepsis hastasını kapsayan retrospektif bir çalışma yapılmıştır. Hastaların demografik verileri, D vitamini ve magnezyum düzeyleri, laboratuvar parametreleri ve klinik skorları (APACHE II, SOFA, SAPS II) başvuru ve taburculuk sırasında toplanmıştır. Bu mikro besin öğeleri ile mortalite arasındaki ilişkiyi değerlendirmek için ki-kare ve korelasyon analizi dahil olmak üzere istatistiksel analizler yapılmıştır.

Bulgular: Sonuçlar, hipomagnezeminin APACHE II ve SOFA dahil olmak üzere daha yüksek klinik ciddiyet skorlarıyla ilişkili olduğunu gösterirken ($p<0,05$), ne D vitamini ne de magnezyum seviyelerinin bağımsız olarak mortaliteyi öngörmediğini göstermiştir. Magnezyum eksikliği daha kötü klinik sonuçlarla ilişkilidir ($p<0.05$) ancak mortalite ile ilişkisi yetersiz kalmıştır ($p>0.05$). Benzer şekilde, düşük D vitamini düzeyleri yaygın olmasına rağmen sağkalımı önemli ölçüde etkilememiştir ($p>0.05$).

Sonuç: D vitamini ve magnezyum düzeyleri sepsis hastalarında mortalite ile bağımsız olarak ilişkili bulunmamıştır. Bununla birlikte, magnezyum eksikliği daha yüksek şiddet skorlarıyla bağlantılı olup, hastalığın ilerlemesindeki potansiyel rolüne işaret etmektedir. Kritik hastalarda bu eksikliklerin düzeltilmesinin terapötik etkilerini keşfetmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: *Sepsis, Vitamin D, Magnezyum, APACHE II, SOFA*

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INTRODUCTION

Septic shock and sepsis are the primary causes of morbidity and mortality in intensive care patients. It creates a significant economic and health burden (Yealy et al., 2021). The annual death rate due to sepsis in the world constitutes 19.7% of all deaths (Rhee et al., 2019; Rudd et al., 2020). In patients in intensive care units; Despite all technological developments and renewed treatment protocols, high mortality rates are still observed (Angus and Van Der Poll, 2013). Prompt identification and management of sepsis are crucial, as it is a time-critical illness that requires early intervention to improve patient outcomes. The search for modifiable risk factors that can influence patient outcomes has led to increased interest in the role of micronutrients, such as vitamin D and magnesium, due to their immunomodulatory and anti-inflammatory properties.

Vitamin D is known for its classic role in calcium and bone metabolism; however, recent evidence highlights its broader biological functions, including regulation of the immune response, modulation of inflammation, and maintenance of the endothelial barrier. Low levels of vitamin D in intensive care patients cause many negative consequences, including infections (Amrein et al., 2014). Despite these associations, clinical trials and observational studies present mixed findings regarding the impact of vitamin D deficiency on sepsis outcomes, with some studies indicating a correlation with increased mortality, while others show no significant effect (Lan et al., 2020; Geiger et al., 2024).

Magnesium is another essential micronutrient with multiple roles in cellular metabolism, energy production, and as a co-factor for numerous enzymatic reactions. They also have important roles in conditions that have a function in the pathophysiology of sepsis, such as cytokine production, immune cell function and cardiac stability (Velissaris et al., 2015; Rosanoff et al., 2021). Hypomagnesemia has been linked to poor clinical outcomes in ICU patients, including prolonged hospital stays, increased severity scores, and higher mortality rates (Gonuguntla et al.,2023; Tonai et al., 2024). However, as with vitamin D, the evidence remains inconclusive regarding the direct impact of magnesium levels on sepsis prognosis. Understanding the interplay between micronutrient deficiencies and critical illness could have important implications for both the prevention and treatment of sepsis, potentially guiding personalized supplementation strategies to improve patient survival and recovery.

With this study, we aimed to evaluate the relationship of magnesium and vitamin D levels with septic shock and sepsis in patients admitted to the tertiary intensive care unit, and to evaluate the correlation of their deficiencies with the severity of the existing disease.

MATERIAL and METHOD

This retrospective study was conducted at the This retrospective study was conducted after obtaining approval from the Ataturk University Faculty of Medicine Local Ethics Committee. following the approval of the hospital's ethics committee (Ethics Committee Approval No: 39, Session No: 01, Date: February 13, 2019). Files and electronic records of 340 patients were examined. The study included a review of the medical records and electronic data of 299 patients diagnosed with sepsis or septic shock who were admitted to the Intensive Care Unit (ICU) of our Anesthesiology and Reanimation Department between January 1, 2017, and January 1, 2019. 41 patients were excluded from the study based on the exclusion criteria.

Patients were identified based on the Sepsis-3 diagnostic criteria outlined by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) (2016 guidelines) and subsequently confirmed for sepsis diagnosis through a reevaluation of these criteria using the recorded data. Patients who met the determined criteria were included in the study. Due to the lack of ScvO2 and cardiac index monitoring, these parameters were not used for diagnosis.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were taken as: Admission to the intensive care clinic due to sepsis and/or septic shock, patients over 18 years of age, were not pregnant, had an ICU stay of more than 24 hours, did not have known renal insufficiency.

The exclusion criteria from the study were taken as: Did not have a diagnosis of sepsis or septic shock, were under the age of 18, were pregnant, stay in intensive care for less than 24 hours, had known chronic renal insufficiency, had incomplete medical records.

Data Collection

The following data were collected for the included patients: demographic characteristics, reasons for ICU admission, Glasgow Coma Scale (GCS) score on the day of admission, levels of procalcitonin (PCT), C-reactive protein (CRP), vitamin D, and magnesium (Mg), as well as the severity scores calculated within the first 24 hours of ICU admission, including the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II (SAPS II). The same parameters (GCS, vitamin D level, Mg level, APACHE II, SOFA, and SAPS II scores) were recorded at the time of ICU discharge, along with the mortality and morbidity outcomes.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22.0. The normality of data distribution was assessed using the Kolmogorov-Smirnov test and histograms. For normally distributed variables the Independent Sample t-test was employed, whereas non-normally distributed data were analyzed using the Mann-Whitney U test. The association between vitamin D and magnesium levels with mortality was evaluated using the chi-square test, while the Wilcoxon signed-rank test was used for score comparisons. Additionally, a correlation analysis was performed to assess the relationship between patient outcomes (discharge or death) and various clinical scores.

RESULTS

A total of 299 patients were hospitalized and treated in intensive care with septic shock and/or sepsis during the period covered by the study. The demographic and laboratory characteristics of these patients at the time of ICU admission are summarized in (Table 1). The mean age of the patients was 68.06 ± 17.17 years, with a nearly equal gender distribution (50.2% male, 49.8% female). The most common comorbid disease was respiratory failure. The mean Glasgow Coma Scale (GCS) score at admission was 8.17 ± 4.65.

A statistically significant difference was found between deceased and living patients in terms of average age, with non-survivors being older on average ($p = 0.017$). No statistically significant differences were noted in vitamin D levels or magnesium levels between survivors and non-survivors at admission and discharge when grouped by age (18-65 years and >65 years) (Table 2).

Patients with vitamin D levels <20 ng/mL did not show a significant difference in severity scores (GCS, APACHE II, SOFA, SAPS II) compared to those with levels >20 ng/mL. However, at ICU discharge, a higher proportion of patients with vitamin D levels <20 ng/mL was observed among non-survivors ($p < 0.001$). Magnesium levels were evaluated, revealing that patients with hypomagnesemia (<1.7 mEq/L) had significantly higher APACHE II and SOFA scores compared to those with normomagnesemia (>1.7 mEq/L), indicating worse clinical outcomes ($p < 0.05$) (Table3 and 4).

Table 1. Demographic and laboratory characteristics at the time of ICU admission

	All patients (n=299)
Age (years)	68.06±17.17
Gender (Male/Female) (%)	150(50.2) /149 (49.8)
Comorbidity (n)	
Respiratory Failure	215
Hypertension	137
Malignancy	85
Diabetes	73
Cerebrovascular Event	49
Cardiac Arrest	38
Other	124
GCS	8.17 ± 4.65
APACHE	25.93 ± 9.25
SOFA	8.59 ± 3.47
SAPSII	59.13 ± 19.06
CRP	113.07 ± 68.85
Procalcitonin	15.02 ± 33.31
Magnesium (mEq/L)	2.09 ± 1.33
D vit (ng/dL)	11.92 ± 14.16

Results were presented as mean ± standard deviation and as number.

Table 2. Comparison of Survivors and Non-Survivors by Age and Gender

	Survivors (n=86)		Non-Survivors (n=213)		P*
Age	63.86±18.72		69.27±16.93		0,017
Sex					
Female	46	(%53.5)	103	(%48.4)	0.422
Male	40	(%46.5)	110	(%51.6)	

Results were presented as mean ± standard deviation and as number. * $P > 0.05$

Analysis showed significant associations between clinical severity scores and patient outcomes. Higher APACHE II, SOFA, and SAPS II scores with increased mortality risk. Vitamin D levels were not significantly correlated with mortality, but lower levels were more frequent in non-survivors. Magnesium levels had a statistically significant association with mortality, particularly in older patients.

Table 3. Comparison of magnesium and vitamin D levels in patients aged 18-65 years and >65 years

		Survivor	Non-Survivor	p
Age 18-65	D vit (t1)	6.9 (0-98)	9.30 (0-92)	0,122
	D vit (t2)	9.95 (1.8-50)	9.2 (0.1-67)	0,709
	Magnesium (t1)	1.90 (1.10-4.60)	1.90 (0-4.10)	0,294
	magnesium (t2)	1.90 (1.10-3.50)	2.1(0.5-3.10)*	**0,016**
Age >65	Vitamin D (ng/dL) (t1)	7.70 (0.80-80)	7.2 (0-49)	0,641
	Vitamin D (ng/dL) (t2)	13.55 (1.1-82)**	9 (0-92)	**0,044**
	Magnesium (mEq/L) (t1)	1.95 (1.40-3.35)	2 (0.99-23)	0,693
	Magnesium (mEq/L) (t2)	1.80 (0.90-2.50)	1.9 (1-3.4)***	**0,016**

All data are presented as median (minimum-maximum). (t1: admission to ICU, t2: discharge)
* p <0.05 In favor of patients who died in the age group under 65
** P < 0.05 In favor of patients over the age of 65
*** p < 0.05 In favor of patients who died in the over 65 age group

Table 4. Scoring systems and biochemical markers according to magnesium levels.

	Hypomagnesemia (<1.7mEq/L) (n=91)	Normomagnesemia (>1.7 mEq/L) (n=208)	P
GKS	7.77±4.64 *	9.09±4.56	0.024
SOFA Score	9.00±3.58 *	7.68±3.07	0.003
APACHEII Score	27.23±9.50 *	22.97±7.94	<0.001
SAPS II	61.42±19.36 *	53.92±17.38	0.002
CRP	115.52±72.08	106.23±61.46	0.285
Procalcitonin	11.22±23.45	15.84±31.63	0.162

All data are presented as median (minimum-maximum)
* P < 0.05 The hospitalization was in favor of hypomagnesemia in terms of GKS, SOFA, APACHE 2, SAPS 2 scores.

DISCUSSION

In this study, vitamin D and magnesium levels and the correlation between the deficiency of these levels and the severity of the disease in patients admitted to the intensive care clinic with the diagnosis of septic shock and/or sepsis were evaluated.

Deficiency of vitamin D, which has an important role in the modulation of the immune system, has been associated with an increased tendency for infections in patients admitted to intensive care and an increase in 30-day mortality rates (Karampela et al., 2024; Wang et al., 2024). On the contrary, our findings revealed that while vitamin D deficiency was prevalent among these patients, its levels were not significantly associated with overall mortality. This observation is consistent with previous studies that reported similar results, where no definitive correlation was established between vitamin D levels and mortality in sepsis patients (Viglianti et al., 2019). In other words, it is not a risk factor for mortality (Aygencel et al., 2013).

Although vitamin D levels were found to be lower in patients over 65 years' old who succumbed during hospitalization, this difference was not statistically significant. This aligns with the literature, suggesting that while older patients are more prone to vitamin D deficiency, the direct impact of this deficiency on sepsis outcomes remains unclear. The fact that vitamin D supplementation did not substantially alter the outcomes further supports the hypothesis that low vitamin D levels might be a consequence rather than a cause of critical illness and sepsis.

Our analysis of magnesium levels indicated a significant association between hypomagnesemia and higher severity scores (GCS, SOFA, APACHE II, and SAPS II) at admission. Patients with low magnesium levels exhibited worse clinical markers, which suggests that magnesium might play a role in the pathophysiological response to sepsis. Previous studies have indicated that magnesium is involved in immune modulation and inflammatory responses, which are crucial in sepsis progression. However, despite its influence on severity scores, hypomagnesemia was not significantly linked to increased mortality in our study, mirroring the findings of other research in critical care settings.

Interestingly, our data showed that magnesium levels increased significantly from admission to discharge in non-survivors. This paradoxical increase in magnesium levels might reflect a compensatory response or a shift due to cellular damage in severe sepsis. This observation warrants further investigation, as the role of magnesium in sepsis remains complex and multifaceted. Our study also highlighted the limitations of using standard severity scores (GCS, SOFA, APACHE II, SAPS II) in predicting outcomes based solely on vitamin D and magnesium levels.

Despite the established role of these scoring systems in estimating patient prognosis, their predictive accuracy was not significantly enhanced by

incorporating vitamin D or magnesium levels, suggesting that other factors might play more critical roles in determining patient outcomes.

The role of magnesium in sepsis appears to be more pronounced. Our study demonstrated that hypomagnesemia was significantly associated with increased APACHE II, SOFA, and SAPS II scores, indicating a higher severity of illness in this group. These findings are supported by current literature (Limaye et al., 2011; Solanki et al., 2022; Laddhad et al., 2023), who reported that low magnesium levels were associated with increased duration of mechanical ventilation, increased days of intensive care unit stay, increased APACHE II scores, and increased mortality rates. Magnesium's crucial role in modulating inflammatory responses, stabilizing cellular membranes, and supporting energy metabolism makes it a vital element in managing critically ill patients, which might account for its stronger association with sepsis severity compared to vitamin D.

Interestingly, while Mg levels did not directly correlate with CRP or procalcitonin levels, its association with clinical severity scores points towards its role as a marker of overall physiological stress rather than a specific inflammatory marker. This observation aligns with the findings of Rubeiz et al. (Rubeiz et al., 1993), where Mg deficiency was linked to increased cytokine production and oxidative stress, further exacerbating multi-organ dysfunction in septic patients.

Our study has several limitations. Firstly, since our study was designed retrospectively, some data were found to be missing during the data review. Secondly, the levels of vitamin D and magnesium were adjusted according to our intensive care unit's routine treatment protocol, and no additional therapeutic modalities were applied to the patients. Thirdly, the impact of cytokines in sepsis on vitamin D and magnesium levels was not evaluated in our study. Due to the limited availability of cytokine levels measured periodically in the retrospective patient data, a complete data analysis could not be performed in these patients. Fourthly, the study was carried out in a third level intensive care clinic with a relatively small sample size of approximately 300 patients, which poses a limitation in terms of generalizability of the results. Lastly, the study group consisted entirely patients with sepsis, preventing a comparison of vitamin D and magnesium levels and mortality analysis in patients admitted to the tertiary intensive care clinic for reasons not related to sepsis.

In conclusion, while vitamin D and magnesium he levels in the patients we included in our study were not primarily associated with mortality rates, their roles in immune function and inflammation suggest they should not be overlooked in clinical practice. The observed trends indicate that these biomarkers may reflect underlying disease processes rather than act as independent prognostic factors. Further research is necessary to clarify their potential therapeutic implications in the management of sepsis.

Ethics Committee Approval

Ethical Issue: Ethical approval of the local ethics committee of Atatürk University Faculty of Medicine (Ethics Committee Approval No: 39, Session No: 01, Date: 13 February 2019).

Conflict of Interest

The authors declare that they have no conflict of interest regarding content of this article.

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Hypocalcemia as a Risk of COVID-19 Mortality: What Level of Hypocalcemia? Direct Measurement or Corrected Calcium Value?

COVID-19 Mortalitesinde Hipokalseminin Rolü: Direkt Ölçüm mü, Düzeltilmiş Kalsiyum mu?

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ABSTRACT

Objective: The negative effects of vitamin D deficiency and hypocalcemia on the frequency and severity of COVID-19 are quite striking. To determine the presence of hypocalcemia in hospitalized COVID-19 patients, the relationship between severity and outcome, and whether albumin correction is necessary to predict this relationship.

Material and Method: Hospitalized COVID-19 patients were grouped for lung involvement, need for intensive care, need for mechanical ventilation, long hospitalization (≥14 days), sepsis, and mortality. Blood calcium, albumin, 25OHvitamin D, parathyroid hormone, phosphorus, and magnesium values and albumin-corrected calcium data were evaluated retrospectively.

Results: The study included 129 hospitalized COVID-19 patients, 67 (51.9%) male and 62 (40%) female. Vitamin D was insufficient in 89.9% of the patients and no association was found with disease severity. Calcium levels were significantly lower in terms of need for intensive care, sepsis, mechanical ventilation and mortality (p: 0.00, 0.013, 0.021, 0.004, respectively). No association was found with corrected Ca (p>0.05 for all). A significant increase was found in the same cases when total Ca values were below 8 mg/dl (p: 0.00, 0.001, 0.005 and 0.001, respectively). In the logistic regression analysis, it was found that age, increase in CRP and decrease in Ca levels significantly increased the risk for mortality (p: 0.005, 0.001 and 0.013, respectively).

Conclusion: It is found that total Ca values obtained by direct measurement below 8 mg/dl in COVID-19 patients were significantly more likely to require intensive care, require mechanical ventilation, sepsis and mortality, and in the analysis we determined that a decrease in direct measured (incorrected with albumin) total Ca values, together with advanced age and high CRP, was an independent risk factor that increased mortality.

Keywords: *COVID-19, Calcium, Corrected calcium, Mortality*

ÖZET

Giriş: D vitamini eksikliği ve hipokalseminin COVİD-19'daki sıklığı ve ciddiyeti üzerine olumsuz etkileri oldukça çarpıcıdır. Hospitalize COVİD-19 hastalarındaki hipokalsemi varlığını, şiddet sonuç ilişkisini ve bu ilişkiyi öngörmede albümin düzeltmesinin gerekli olup olmadığını belirlemek.

Materyal ve Metot: Yatan COVİD-19 hastaları akciğer tutulumu, yoğun bakım ihtiyacı, mekanik ventilasyon ihtiyacı, uzun yatış (≥14gün), sepsis, mortalite için gruplandırıldı. Kan kalsiyum, albümin, 25OHvitamin D, parathormon, fosfor ve magnezyum değerleri ile albüminle düzeltilmiş kalsiyum verileri retrospektif değerlendirildi.

Bulgular: Çalışmaya 67 (51.9%) erkek ve 62 (40%) kadın hasta olmak üzere 129 hospitalize COVİD-19 hastası alındı. Hastaların 89.9%'unda D vitamini yetersizdi ve hastalık şiddeti ile bir ilişki saptanmadı. Kalsiyum düzeyleri; yoğun bakım ihtiyacı, sepsis, mekanik ventilasyon ve mortalitede anlamlı olarak düşük tespit edilmiştir (sırası ile p: 0.00, 0.013,0.021, 0.004). Düzeltilmiş Ca ile bir ilişki saptanmadı (hepsinde p>0.05). Total Ca değeri 8mg/dl altında yine aynı durumlarda anlamlı olarak artış tespit edildi (sırası ile p:0.00, 0.001, 0.005 ve 0.001). Logistik regresyon analizinde mortalite için yaş, CRP artışı ve Ca düzeylerinde düşmenin anlamlı risk artışı yaptığı saptandı (sırası ile p: 0.005, 0.001 ve 0.013).

Sonuç: COVİD-19 hastalarında direkt ölçüm ile elde edilen total Ca değerinin 8 mg/dl nin altında olmasını yoğun bakım ihtiyacı, mekanik ventilasyon ihtiyacı, sepsis ve mortalitede anlamlı olarak daha fazla bulduk ve yapılan analizde direkt ölçüm (albumin ile düzeltilmemiş) total Ca değerinde düşmenin, ileri yaş ve CRP yüksekliği ile birlikte mortaliteyi artıran bağımsız bir risk faktörü olduğunu belirledik.

Anahtar kelimeler: *COVİD-19, Kalsiyum, Düzeltilmiş kalsiyum, Mortalite*

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INTRODUCTION

The COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that started in December 2019 has spread rapidly globally. 761,402,282 people have been infected with this virus worldwide. It is estimated that 1-20% of the world's population has been exposed to COVID-19. The number of infected people is beyond estimates, as many patients are asymptomatic and have not been tested. There has been a great loss of life due to COVID-19. As of March 19, 2023, the number of deaths reported to the World Health Organization is 6,887,000 (WHO, 2023). Various studies have been published to determine the risk factors for poor prognosis of this devastating viral disease (Carpagnano, 2020; Di Filippo, 2020; Lippi, 2020; Ponti, 2020; Ahmet, 2021). The negative effects of vitamin D deficiency and hypocalcemia on the frequency and severity of this disease are quite striking.

Vitamin D has been shown to play an important role in immune system activation and prevention of infections. Vitamin D receptors are found in many cells of the immune system, such as macrophages, dendritic cells, and T and B cells. It has been shown that there is an increase in respiratory system diseases, influenza, and M. tuberculosis infections in those with vitamin D deficiency (Mao, 2020). In a retrospective observational study conducted in Italy and including patients with severe COVID-19, it was found that patients presenting with severe vitamin D deficiency had a significantly higher short-term mortality risk (Carpagnano, 2020).

It has been reported that calcium is used by the virus by participating in the replication mechanisms in SARS-CoV-2 infection, also known as COVID-19, just as it has been shown in Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Ebola virus infections (Millet, 2018; Nathan, 2020; Straus, 2020). In line with this, hypocalcemia has been a prominent finding in COVID-19 patients with pneumonia (Crespi, 2020). Diez et al. have shown that a decrease in calcium levels causes an increase in the need for mechanical ventilation, the need for intensive care, hospital mortality and the risk of combined outcome (Diez, 2022).

In our study, we specifically investigated the presence of hypocalcemia in COVID-19 patients, its relationship with the clinical course of COVID-19, and whether albumin correction was necessary to predict this relationship. We also checked the blood levels of 25-OH vitamin D, which plays a role in Ca metabolism and is an immune system regulator and anti-inflammatory hormone, and PTH, P and Mg, which also affect and are affected.

MATERIAL and METHOD

The study was conducted as a retrospective cohort on the records of 129 patients who were hospitalized in the wards and intensive care units of Van Yuzuncu Yil University Medical Faculty Hospital due to COVID-19 between 01.10.2021-01.02.2022. Samples were taken from upper respiratory tract samples (nose or throat) with a swab and studied with RT-PCR in Van YYU Hospital Clinical Microbiology Laboratory. Patients who were diagnosed with COVID-19 and had positive RT-PCR or antibody tests were included in the study.

Laboratory markers (creatinine, albumin, Ca, Mg, P, vitamin D, PTH, ferritin, CRP), vital signs (fever, O_2 saturation, blood pressure, pulse, respiratory rate) and lung Computed Tomography and direct radiography images important in the prognosis of COVID-19 were obtained from the hospital's computer system.

Groupings made in our study:

1-) Female and male

2-) Hospitalized patients' need for ward or intensive care

3-) Patients' survival status according to whether they are alive or dead

4-) Patients' sepsis and non-sepsis according to qSOFA criteria

5-) Patients' need for mechanical ventilation and non-sepsis

6-) Hospitalization period of 14 days and above and those who are not

7-) According to 25OHvitamin D level; sufficient (≥30ng/ml), insufficient (20-29ng/ml), deficient (10-19ng/ml) and profoundly deficient (<10ng/ml)

8-) According to calcium level; hypocalcemia (<8.5mg/dl), significant hypocalcemia (<8mg/dl) 'qSOFA criteria' are criteria used in the bedside assessment of adult patients with suspected infection for sepsis in out-of-hospital, emergency department or general hospital settings.

There are 3 parameters.

1- Tachypnea(>22/min)

2- Hypotension(<100mmHg)

3- Mental changes

The presence of 2 or more of the 3 criteria suggests sepsis (Vincent, 2016).

25-OH vitamin D measurement was performed by a chemiluminescence method using 25-OH D commercial kit (Elecsys) in our hospital. Results are given as ng/ml. The normal value of serum 25-OH D was accepted as ≥30 ng/ml (Chauhan, 2023).

Calcium levels were recorded by direct measurement and corrected Ca calculation. The normal value range of calcium level is 8.5 to 10.3 mg/dL. It is free, ionized extracellular calcium that affects all physiological functions. It was calculated with the formula Corrected calcium (mg/dl) = (4-serum albumin) x0.8 + measured total calcium (mg/dl) (Benabel, 1994). The normal value range of magnesium level is 1.7 to 2.3 mg/dL. The normal value range of phosphorus level is 2.5-4.5 mg/dl (0.81-1.45 mmol/l). The normal value range for PTH levels is 15-65 pg/mL.

Statistical analysis

In calculating the sample size of this study, Power (Test Power) was determined for each variable by taking at least 80% and Type-1 error as 5%. Kolmogorov-Smirnov (n>50) and Skewness-Kurtosis tests were used to check whether the continuous measurements in the study were normally distributed, and since the measurements were normally distributed, parametric tests were applied. Descriptive statistics for the variables in the study were expressed as mean, standard deviation, minimum, maximum, number (n) and percentage (%). Chi-square test was used to compare measurements according to "categorical groups", and "Independent T-test" was used to compare parametric groups. Logistic Regression analysis was used to determine (estimate) the effect of some variables on "mortality". Pearson correlation coefficients were calculated to determine the relationship between measurements. In the calculations, the statistical significance level (á) was taken as 5% and SPSS (IBM SPSS for Windows ver. 25) statistical package program was used for the analysis

RESULTS

Of the 129 patients included in the study, 67 (51.9%) were male and 62 (40%) were female. In 116 of 128 patients (89.9%), 25OH vitamin D levels were found to be below 30ng/ml. Magnesium and creatinine were significantly lower in women than in men (p: 0.025, 0.001, respectively). (Table 1)

Table 1. Comparison of parameters between genders

	Gender				
	Female (N:62)48.1%		**Male (N:67) 51.9%**		***p**
	Mean	**Std. Dev.**	**Mean**	**Std. Dev.**	
Age	60.69	15.69	59.79	13.93	.730
25 OH vitamin D (ng/ml)	16.16	22.61	14.76	15.39	.680
PTH (pg/ml)	124.7	76.47	104.56	70.18	.143
Ca (mg/dl)	7.93	.71	7.75	.64	.138
Mg (mg/dl)	1.96	.31	2.07	.23	.025
P (mg/dl)	2.92	.82	2.77	.65	.267
Albumin (g/l)	4.23	5.76	3.19	.56	.151
Ferritin (ng/ml)	834.09	1841.90	1127.77	1203.72	.282
Crp (mg/l)	57.03	67.87	59.05	54.46	.853
Creatinine (mg/dl)	.73	.21	.85	.22	.001
O_2 Saturation (%)	89.68	6.86	89.18	7.57	.697
Duration Covid (days)	13.81	7.63	10.81	9.42	.050
Corrected Ca	8.59	.56	8.44	.59	.142

** Significance levels according to Independent T-test results*

Of the 129 patients, 47 (36.4%) were intensive care patients and 82 (63.5%) were ward patients. Of the intensive care patients, 26 (61.9%) were male and 16 (38%) were female. When intensive care patients were compared with ward patients; COVID-19 disease duration was significantly longer and the mean age was higher in the intensive care unit (p: 0.001, 0.031, respectively). Oxygen saturation of intensive care patients was significantly lower (p: 0.000). Ferritin and CRP were significantly higher in intensive care patients (p: 0.012, 0.000, respectively). PTH levels of intensive care patients were significantly higher than ward patients (p: 0.000). Ca levels of intensive care patients were significantly lower than ward patients (p: 0.000). (Table 2)

Table 2. Comparison of ward and intensive care patients

	Group				
	Ward (N:82 63,6%)		Intensive Care (N:47 36,4%)		*p
	Mean	Std. Dev.	Mean	Std. Dev.	
Age	58.11	14.21	63.91	15.09	.031
25 OH vitamin D	14.75	19.36	16.60	18.81	.601
PTH	95.44	58.05	145.33	86.29	.000
Ca	7.99	.63	7.56	.66	.000
Mg	2.02	.27	2.01	.29	.762
P	2.88	.75	2.78	.73	.496
Albumin	3.86	4.21	3.38	3.66	.521
Ferritin	729.34	879.78	1435.51	2225.17	.012
Crp	43.22	44.88	84.55	76.07	.000
Creatinine	.81	.20	.77	.26	.338
O_2 Saturation	91.23	4.64	86.26	9.53	.000
Duration Covid	10.40	5.73	15.47	11.68	.001
Corrected Ca	8.51	.55	8.51	.63	.981

** Significance levels according to Independent T-test results*

When patients with pulmonary involvement (n: 101, 78%) were compared with those without (n: 23, 22%), only CRP was found to be significantly higher in those with involvement (p: 0.02 63.5 mg/l vs 31.5 mg/l). In the statistical analysis performed between genders, no significant difference was found in terms of pulmonary involvement, mortality and sepsis (p: 0.105, 0.567, 0.478, respectively). When we compared those with a hospital stay of 14 days (n:42) or more (n:87) with those without, age, 25OH vitamin D, PTH, Ca, Mg, albumin, ferritin, CRP, creatinine and O_2 saturation levels were found to be similar (p: 0.34, 0.42, 0.80, 0.90, 0.11, 0.83, 0.66, 0.06, 0.35 and 0.14, respectively). Albumin-corrected Ca and P were found to be significantly higher in those with a longer hospital stay (p: 0.025, 0.006, respectively).

According to qSOFA criteria, when patients with sepsis (n: 57) were compared with those without (n: 72), PTH was significantly higher and Ca was significantly lower in sepsis (p: 0.024, 0.013, respectively). (Table 3)

Table 3. Comparison of laboratory parameters between sepsis and non-sepsis patients

	qSOFA (Sepsis)				
	No (N:72, 55,8%)		Yes (N:57, 44.18%)		p*
	Mean	Std Dev.	Mean	Std Dev.	
Age	58.46	14.71	62.46	14.63	.127
25-OH vitamin D	16.28	21.14	14.37	16.35	.575
PTH	100.32	63.12	130.78	82.31	.024
Ca	7.97	.53	7.67	.80	.013
Mg	2.04	.26	1.99	.30	.339
P	2.93	.74	2.73	.73	.136
Corrected Ca	8.48	.44	8.56	.73	.464

** Significance levels according to Independent T-test results*

The number of patients requiring mechanical ventilation was 30 and the number of patients not requiring mechanical ventilation was 99. In the statistical analysis, the mean age was 64 in those intubated and 59 in those not (p: 0.095). Again, PTH was higher in those requiring mechanical ventilation, but it was not statistically significant (mean: 135 vs 107pg/ml, respectively, p: 0.085). 25OHvitamin D, Mg, P and corrected Ca values were also found to be statistically insignificant (p: 0.84, 0.34, 0.96, 0.97, respectively). Calcium levels were significantly lower in those requiring mechanical ventilation than in those not (mean: 7.58 vs 7.91 mg/dl, respectively, p: 0.021)

Thirty-eight (80.8%) of the intensive care patients and 1 (1.2%) of the ward patients were COVID-19 mortal. When the deceased (n: 39) and surviving (n: 90) patients were compared; age, disease duration, CRP level and PTH level were found to be significantly

higher in mortality (p: 0.002, 0.000, 0.000, 0.003, respectively), while oxygen saturation and Ca level were found to be significantly lower (p: 0.000, 0.004, respectively). (Table 4)

Table 4. Comparison of data of mortal and surviving patients

	Alive (N:90 69,76%)		Mortal (N:39 30,24%)		*p
	Mean	Std. Dev.	Mean	Std. Dev.	
Age	57.56	14.41	66.38	13.80	.002
Vitamin D	15.74	21.57	14.72	11.91	.781
PTH	100.93	64.39	143.74	84.95	.003
Ca	7.95	.65	7.57	.67	.004
Mg	2.02	.26	2.01	.31	.982
P	2.87	.73	2.79	.77	.615
Albumin	3.76	4.05	3.52	3.97	.762
Ferritin	848.37	1496.01	1305.68	1626.10	.123
CRP	43.99	44.57	91.43	80.03	.000
Creatinine	.78	.19	.81	.28	.611
O_2 Saturation	91.11	4.80	85.51	9.94	.000
Duration-Covid	10.52	5.84	16.23	12.33	.000
Corrected Ca	8.52	.55	8.49	.65	.812

** Significance levels according to Independent T-test results*

In the correlation analysis, a significant, inverse and low-level relationship was found between CRP and Magnesium in ward patients (r=-0.249). This relationship was also present in intensive care patients (r=-0.044). In addition, in this patient group, a significant, positive relationship was found between phosphorus and magnesium levels (r=0.333) and a significant, negative relationship was found between CRP and vitamin D (r=-0.038).

All patients were grouped as profound deficiency (<10ng/ml), deficiency (10-19ng/ml), insufficiency (20-29 ng/ml) and sufficient (≥30ng/ml) according to their 25OH vitamin D levels. Mortality was 46.1% at vitamin D levels ≥30ng/ml, 36.3% in the range of 20-29 ng/ml, 26.8% in the range of 10-19 ng/ml and 28.57% below 10 ng/ml and it was not found statistically meaningful (p: 0.56). In the statistical analysis, although the numbers of the sufficient and insufficiency groups were low, no significance was found for the presence of pulmonary involvement and sepsis. The same result was reached in the comparison of the deficiency and profound deficiency groups with sufficient numbers for the same parameters (p: 0.49, 0.51, 0.25, respectively). (Table 5)

Table 5. Comparison of groups according to 25OH vitamin D levels for pulmonary involvement, mortality, sepsis and need for mechanical ventilation

		<10ng/ml	10-19ng/ml	20-29ng/ml	≥30ng/ml	Total	p *
Pulmonary involvement	**No**	13	8	2	0	23	0.33
	Yes	47	33	8	13	101	
Mortal	**No**	45	30	7	7	89	0.56
	Yes	18	11	4	6	39	
qSOFA(sepsis)	**No**	33	25	7	6	71	0.68
	Yes	30	16	4	7	57	
Need for mechanical ventilation	**No**	49	33	8	8	98	0.54
	Yes	14	8	3	5	30	
Hospitalization period≥14 days	**No**	43	31	7	5	86	0.099
	Yes	20	10	4	8	42	

**Chi square test*

Patients with hypocalcemia were divided into two groups as Ca value <8mg/dl and <8.5mg/dl and analyzed for gender, age, clinical need, long hospitalization period (≥14 days), lung involvement, mortality, sepsis and mechanical ventilation need. A significant increase in the need for intensive care, mortality, sepsis and mechanical ventilation need was found only in the group with significant hypocalcemia (Ca <8mg/dl) (p: 0.000, 0.001, 0.001, 0.005, respectively). The mortality rate was 32% in Ca <8.5mg/dl and 41.6% in <8mg/dl. No relationship was found with age in either the Ca <8.5mg/dl or <8mg/dl groups (p: 0.92, 0.27, respectively). Additionally, when we analyzed the hypocalcemia and profound hypocalcemia groups for the under 50 age group and the over 50 age group, no significance was found (p: 1 and 0.83, respectively). (Table 6)

When we made the same grouping with albumin-corrected Ca values, although it was not significant when the value was below 8 mg/dl, a result close to significance was obtained in need of intensive care, need for mechanical ventilation and mortality (p: 0.068, 0.075, 0.056, respectively). No significance was found in the analysis for age, gender, need for intensive care, sepsis, lung involvement, mortality, mechanical ventilation, and prolonged hospitalization in the corrected calcium group of threshold value 8.5 (p: 0.35, 0.36, 0.85, 0.71, 0.63, 0.56, 0.4 and 0.44). No significance was found in the analysis for age, gender, sepsis, lung involvement and prolonged hospitalization in the corrected group of threshold value 8 (p: 0.63, 0.14, 0.45, 0.75 and 0.6, respectively).

Table 6. Comparison of groups with calcium values below 8.5 mg/dl and 8 mg/dl

		Ca<8mg/dl (56.25%)		P*	Ca<8.5mg/dl (82.8%)		P*
		Yes (n)	No (n)		Yes (n)	No (n)	
Gender	**Female**	30	32	0.059	48	14	0.059
	Male	42	24		58	8	
Long hospital stay	**No**	48	39	0.849	73	14	0.849
	Yes	24	17		33	8	
Clinical need	**Ward**	36	46	0.000	65	17	0.000
	Intensive Care	36	10		41	5	
Pulmonary Involvement	**No**	11	12	0.364	16	7	0.364
	Yes	59	42		87	14	
Mortal	**No**	42	48	0.001	72	18	0.001
	Yes	30	8		34	4	
qSOFA (sepsis)	**No**	31	41	0.001	58	14	0.001
	Yes	41	15		48	8	
Need for mechanical ventilation	**No**	49	50	0.005	81	18	0.005
	Yes	23	6		25	4	

**Chi square test*

In Model 1, established for the dependent mortality rate, age and CRP levels have a significant effect in distinguishing mortality. It can be said that increasing age and CRP levels increase the probability of mortality.

In Model 2, age, CRP and calcium levels have a significant effect in distinguishing the mortality situation. It can be said that increasing age and CRP levels increase the probability of mortality. Low calcium also increases the probability of mortality (B=-0.934). (Table 7)

Table 7. Determination of variables that may have an impact on "mortality frequency"

			S.E.	Wald	p.	Odds	95% Safe Search	
							Bottom	Top
Step 1	**Age**	.043	.018	5.465	.019	1.044	1.007	1.082
	PTH	.003	.004	.570	.450	1.003	.996	1.010
	Ca	-.793	.419	3.590	.058	.452	.199	1.028
	CRP	.015	.004	11.756	.001	1.015	1.007	1.024
	Steady	1.393	3.384	.169	.681	4.027		
Step 2	**Age**	.048	.017	7.956	.005	1.049	1.015	1.085
	Ca	-.934	.378	6.119	.013	.393	.187	.824
	CRP	.015	.004	11.603	.001	1.015	1.007	1.024
	Steady	2.484	3.063	.658	.417	11.990		

**Logistic Regression Analyse.*

DISCUSSION

Calcium ion is one of the most common molecules involved in signal transduction in almost all cellular processes. Again, in viral infections, it is an ion used in almost every stage of the virus life cycle, such as the formation of the virion structure, entry of the virus into the cell, viral gene expression, formation of virus proteins, virion maturation and release from the cell (Zhou, 2009). In our study, calcium levels of hospitalized COVID-19 patients were found to be significantly lower in the group requiring intensive care, the group with sepsis, the group requiring mechanical ventilation and the group with a mortal course.

In the case-control studies of Cappellini et al., a significant relationship was reported between COVID-19 positivity, male gender, advanced age and low calcium (Cappellini, 2020). In our study, we did not find a relationship between age and calcium. However, in male gender, we found calcium below 8 mg/dl at a level close to significance (p: 0.059).

Many studies have shown the presence of hypocalcemia during the course of COVID-19 infection (Lippi, 2019; Di Filippo, 2020, Crespi, 2020; Diez, 2023). In most of the existing studies, the hypocalcemia threshold value was taken as 8.8 mg/dl (2.2 mmol/l), 8.6 mg/dl (2.15 mmol/l) or 8.5 mg/dl (2.12 mmol/l) by correction with albumin or direct measurement, and the prevalence of hypocalcemia was reported between 62.6% and 74.7% according to these threshold values (Cappellini, 2020; Sun, 2020; Tezcan, 2020; Torres, 2020; Wu, 2020; Zhou X, 2020; Bennouar, 2021; Hernandez, 2021; Liu, 2020; Pal, 2021). In our study, where we took the Ca threshold value as 8.5 mg/dl, we detected a higher rate of hypocalcemia in cases hospitalized due to COVID-19, with 82.8%. This rate was 79.2% in ward patients and 89.1% in intensive care patients. This situation can be explained by the use of Ca by the virus, as well as vitamin D deficiency, impaired intestinal absorption, hypoalbuminemia and increased fatty acids due to stress.

In a study where the hypocalcemia threshold value was taken as 2.2 mmol/l (8.8 mg/dl), its relationship with the need for long hospitalization was reported, while in another study where the same threshold value was used, hypocalcemia was seen significantly more in COVID-19 patients with severe clinical picture compared to mild-moderate clinical picture (84% vs. 49%) and this was reported to be related to increased interleukin-6 (Wu, 2020; Zhou 2020). We took 8.5 mg/dl (2.12) as the hypocalcemia threshold for grouping and below 8 mg/dl, which we can interpret as significant hypocalcemia. Although we did not detect any relationship in this direction in the hypocalcemia group with the threshold value of 8.5 mg/dl, we found that this situation increased at a level close to significance in the group with lung involvement (p: 0.06).

In a retrospective study by Sun et al., it was observed that the incidence of multiple organ failure, septic shock, and 28-day mortality were significantly higher in those with calcium levels below 2 mmol/l (8.02 mg/dl). The authors did not correct serum calcium levels according to serum albumin levels (Sun et al., 2020). In line with this study, we found that there was a significant increase in the need for intensive care, the need for mechanical ventilation, mortality, and sepsis in the hypocalcemia group below 8 mg/dl, which we detected by direct measurement. We also found that a decrease in calcium was a significant risk factor for mortality.

In a case-control study, albumin-corrected Ca was found to be significantly lower in COVID-19 patients than in controls, but its relationship with disease severity was not reported (Hernandez, 2021). Again, Tezcan et al. detected hypocalcemia with a corrected Ca value below 8.5 mg/dl in 21.5% of severe COVID-19 cases and did not report it as a risk for poor prognosis (Tezcan, 2019). In another study, hypocalcemia was detected in 35% of cases with a corrected Ca value below 2.05 mmol/l and was reported to be an indicator of poor prognosis (Bennouar, 2021). Liu J et al. also detected hypocalcemia with a corrected Ca value below 2.15 mmol/l in 62.6% of severe COVID-19 patients and reported that hypocalcemia was an important risk factor for poor prognosis for any of the outcomes of mechanical ventilation, need for intensive care or mortal results (Liu, 2020). Torres et al. also studied hypocalcemia in hospitalized COVID-19 patients with corrected Ca measurement below 8.5 mg/dl and showed that this was only associated with the need for intensive care (Torres, 2020).

In the study by Diez et al., both direct measurement Ca and corrected Ca values were compared in mechanical ventilation requirement, intensive care requirement, hospital mortality and combined outcome groups and while direct measurement was found to be significantly lower in each group, it was found that corrected Ca value was significantly lower only in mortality compared to direct measurement (p: 0.02 vs 0.001, respectively) (Diez, 2023). In our study, we also found that the value obtained with direct total calcium measurement was significantly lower in intensive care requirement, sepsis, mechanical ventilation requirement and mortality. However, we did not find any significance with corrected Ca value.

Regarding the 25OH vitamin D levels that should be checked in relation to calcium metabolism; Hernandez JL. et al. found vitamin D levels below 20 ng/ml in 82.2% of the patients in their retrospective case-control study and significantly lower than the control group, and did not report any relationship with disease severity except for prolonged hospitalization (Hernandez, 2021). Bennouar et al. also found hypovitaminosis D (<39 nmol/l-15.6 ng/ml) in 75% of severe COVID-19 cases in their study and reported that it was lower in men than in

women (Bennouar, 2021). In our study, we found vitamin D levels below 20 ng/ml in 82% of the cases, below 30 ng/ml in 89.8%, and below 10 ng/ml in 49%. Our rates are consistent with Hernandez's study. We found that the 25 OH vitamin D blood levels of intensive care patients and ward patients were statistically similar, and the results were similar for both genders, too. In a large meta-analysis including 1368 COVID-19 cases, it was reported that vitamin D deficiency was associated with poor prognosis (Munshi, 2020). In our study, when patients were grouped as sufficient, insufficient, deficient, and profoundly deficient according to their 25 OH vitamin D levels and compared statistically for pulmonary involvement, need for intensive care, need for long-term hospitalization, sepsis, and mortality, the levels were found to be insignificant in determining clinical severity. The fact that most of our patients had inadequacy in this result may be a factor.

We found PTH, another factor that plays an important role in calcium metabolism, to be high in 72.1% of our patients. In addition, PTH levels were significantly higher in sepsis, the need for intensive care, and mortality. However, when evaluated as a risk factor for death with logistic regression analysis, age, high CRP, and hypocalcemia were determined as significant risk factors. Finally, we did not find any significance in the evaluation of P and Mg levels. Both et al. showed that 53% of SARS-infected patients had hypophosphatemia, 57% had hypomagnesemia, and 70% had hypocalcemia (Booth, 2003). Our rates of hypomagnesemia and hypophosphatemia in the ward and intensive care patient groups were lower than in this study (13.4% vs. 14.2% and 32.9% vs. 31.9%, respectively), and hypocalcemia was higher.

The relatively limited number of cases in our study, the fact that it was a cross-sectional study and that healthy controls were not used are factors that weaken its power. A well-organized prospective study with replacement of deficiencies and a large number of cases may demonstrate the clinical benefit of this data.

In conclusion, we found that total Ca values below 8 mg/dl obtained by direct measurement without albumin correction in COVID-19 patients significantly increased the need for intensive care, the need for mechanical ventilation, sepsis and mortality, and in our analysis, we found that advanced age and high CRP values, along with a decrease in directly measured total Ca values, were independent risk factors that increased mortality. Our study suggests that correction with albumin may not be necessary when evaluating Ca levels in COVID-19 patients and that Ca replacement may be appropriate for directly measured Ca values below 8 mg/dl. In addition, these results can be taken into consideration in critically ill patients with other viral infections.

Conflict of interest: The authors have no conflicts of interest to report.

Ethical approval: This study was approved by the Van Yuzuncu Yil University Non-Interventional Clinical Research local ethics committee on 10.09.2021 with the decision number 2021/10-08.

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Ketogenic Diet and Cancer

Ketojenik Diyet ve Kanser

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ABSTRACT

The ketogenic diet is a diet implemented with high fat consumption and adequate protein by reducing glucose and increasing ketone bodies. Ketogenic diet: it is recommended as an effective intervention on diseases such as diabetes, obesity, cardiovascular diseases and cancer. The ketogenic diet is a diet with high fat and low protein by reducing glucose and increasing ketone bodies. Ketogenic diet: it is recommended as an effective intervention on diseases such as diabetes, obesity, cardiovascular diseases and cancer. In experimental models and clinical studies, the ketogenic diet has an antitumor effect by reducing energy sources to cells and preventing tumor growth. Cancer cells use the Warburg effect on ketogenic diet metabolism. Aerobically dominant glucose utilization may be a possible pathway to be targeted during cancer therapy. Research emphasizes that the integration of the ketogenic diet with the traditional treatment protocol will show positive results on the antitumor effect of chemotherapy. This review provides evidence for understanding the mechanism of action of the ketogenic diet on cancer treatment and its therapeutic use

Keywords: *Cancer, Ketogenic diet, Antitumor, Warburg effect.*

ÖZET

Ketojenik diyet, glikozu azaltıp keton cisimlerini arttırarak yüksek yağ kullanımı ve yeterli miktarda protein ile uygulanan bir diyettir. Ketojenik diyet; diyabet, obezite, kardiyovasküler rahatsızlıklar ve kanser gibi hastalıklar üzerinde etkili bir müdahale olarak önerilmektedir. Deneysel modellerde ve klinik çalışmalarda ketojenik diyet, hücrelere giden enerji kaynaklarını azaltıp tümör büyümesini engelleyerek, antitümör etki göstermektedir. Kanser hücreleri ketojenik diyet metabolizması üzerinde Warburg etkisini kullanmaktadır. Aerobik olarak baskın glikoz kullanımı, kanser tedavisi sırasında hedef alınması gereken muhtemel bir yol olabilir. Araştırmalar ketojenik diyetin, uygulanan geleneksel tedavi protokolü ile bütünleşmesinin kemoterapinin antitümör etkisi üzerinde olumlu sonuçlar göstereceğini vurgulamaktadır. Bu derleme, ketojenik diyetin kanser tedavisi üzerindeki etki mekanizmasını anlamak ve terapötik olarak kullanımına ilişkin kanıtlar sunmaktadır.

Anahtar kelimeler: *Kanser, Ketojenik diyet, Antitümör, Warburg etkisi.*

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INTRODUCTION

Ketogenic diet; it is a diet approach based on minimal carbohydrate intake and excessive fat intake, which causes weight loss, provides mental relaxation and increases energy levels (O'Neill and Raggi, 2020). In this diet, which increases fat and protein intake and reduces carbohydrate consumption, fat is used as the body's primary fuel source, which activates the metabolic process called ketosis (Masood et al., 2023). In this way, the body can keep enough calories for daily activity. The main purpose of this diet is to reduce the fat rate in the body and improve the metabolic health of the body in a positive way (Ding et al., 2019; O' Neill and Raggi, 2020). In recent studies on ketogenic diet; it has been stated that it has benefits on many diseases such as reversing the symptoms of metabolic syndrome, improving the epigenetic profile, changing the microbiome, reducing or eliminating the insulin requirements of type II diabetic patients, increasing brain function and reducing the risk of cancer (Dowis and Banga, 2021). The ketogenic diet has recently been proposed as an adjuvant therapy in cancer treatment (Klement, 2019). The effect of the ketogenic diet as an adjuvant for cancer is based on the mechanism of the Warburg effect (Weber et al., 2018). The Warburg effect is based on the process of cancer cells providing ATP, which is used as an energy source, through glycolysis, unlike oxidative phosphorylation. In this way, the ability of some cancer cells to metabolize ketone bodies is lost. Ketosis occurs when cells are unable to obtain energy through glycolysis. This causes a decrease in insulin and similar growth factors, which are among the factors that cause the increase of cancer cells (Yang et al., 2021). Recent studies have shown that the ketogenic diet has a curative effect on tumor control in glioma, pancreatic cancer, lung cancer, breast cancer and prostate cancer (Zhao et al., 2022). It has also been stated that it is not only effective on tumor growth, but also plays a role in making other cells less affected by radiotherapy and chemotherapy treatments (Klement, 2019). It can be predicted that this diet, which has proven beneficial effects, will provide improvements both in supporting cancer treatment and in improving the quality of life of cancer patients. This study conducted a systematic review to better understand the ketogenic diet and provide more information about its effectiveness as an adjuvant treatment for cancer.

Physiology of the ketogenic diet

The principle of the ketogenic diet consists of reducing carbohydrate consumption by keeping fat and protein intake higher. With this diet, carbohydrate intake decreases to less than 50 g per day (Shilpa and Mohan, 2018). In carbohydrate deprivation, insulin secretion decreases and glycogen stores in the body are depleted. The body activates the metabolic process of gluconeogenesis and ketogenesis to provide a different energy source (Masood et al., 2023). Gluconeogenesis can be sustained for three days in the presence of a ketogenic diet, but when glucose production decreases, endogenous breakdown of glucose cannot provide sufficient energy. To meet the metabolic requirements of the body and brain, the process of ketogenesis begins to obtain an alternative energy source in the form of ketone bodies. In this case, ketone bodies are used as the primary energy source (Batch et al., 2020; Hernandez, 2021). Ketone bodies are produced in the liver as acetoacetate and β-hydroxybutyrate. These primary ketone bodies accumulate in the body and are used as an energy source in the presence of a ketogenic diet. Since ketone bodies are formed as a result of the breakdown of fats, ketosis is one of the safest parameters of fat loss (Shilpa and Mohan, 2018; Masood et al., 2023). Ketone bodies synthesized in the body can be used as an energy source by the heart, muscle tissue and kidneys, and can also provide alternative energy to the brain by passing the blood-brain barrier (Dhillon and Gupta, 2023).

Effect of ketogenic diet on cancer

Cancer is one of the most important challenges people face. Cancer occurs as a result of mutations in many genes that regulate cell growth and proliferation (Golemis et al., 2018). These mutations may be due to many reasons such as DNA replication defects, errors in DNA repair mechanisms, exposure to mutagens, and increase in reactive oxygen species (Dowis and Banga, 2021). Preventive mechanisms for cancer will aim to eliminate these causes or reduce cellular errors. Another underlying cause of deaths caused by cancer is obesity and overweight (Dowis and Banga, 2021). The role of obesity in cancer is the increase in fat cells in the body. In this way, insulin and insulin growth factor 1 (IGF1) hormones increase. These hormones activate signaling pathways that aim for greater cell survival and regulate transcription factors that have an important role in cell proliferation, as shown in Fig.1 (Font-Burgada et al., 2016). These two hormones increase the glucose level in the cells and provide the energy molecules required for cell growth. While insulin supports glucose uptake into cells, it also inhibits liver ketone production. Research conducted have shown that the increase in serum insulin level supports the growth of cancer cells (Gunter et al., 2015; Bolla et al., 2019; Dowis and Banga, 2021). It is inevitable that the diet can have a great impact on eliminating the risk of cancer, especially considering that it reduces body weight, reduces insulin levels and targets the metabolic weaknesses of cancer cells (Dąbek et al., 2020). While reducing the use of glucose through diet starves the cancer cell, ketone bodies become available for the energy needs of normal cells.

Another effect is that it reduces insulin and insulin-like growth factors that help cancer proliferate (Dąbek et al., 2020; Dowis and Banga., 2021). Ketogenic diet; it has shown its therapeutic effect on neuroblastoma, acute myeloid leukemia and glioblastoma tumors thanks to its ability to reduce GPR109A (nicotinic acid G-protein coupled receptor) expression, activate mTORC1 (Mammalian Target of Rapamycin Complex 1) and reduce glucose uptake in the tumor (Tobias et al., 2015).

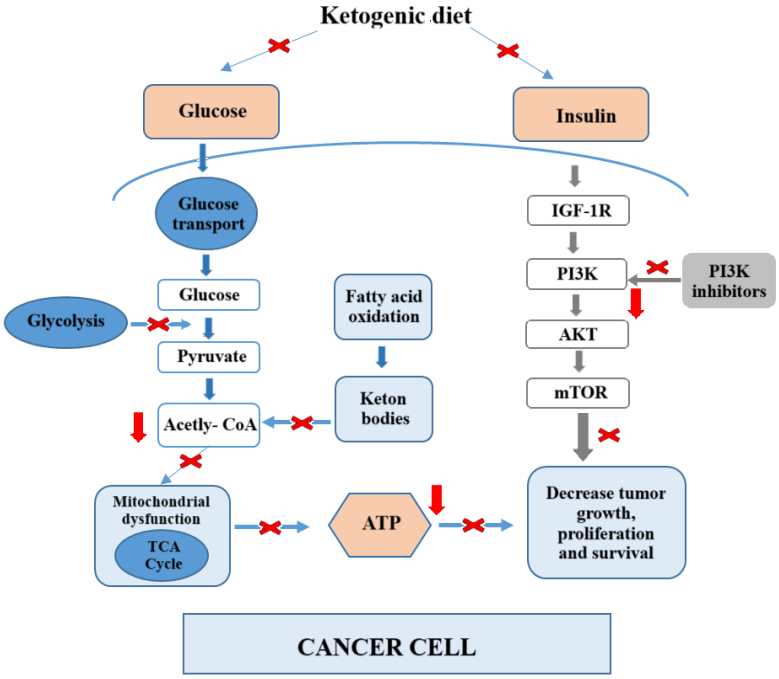

Figure 1. Effect of ketogenic diet on cancer cells. IGF-1R: Insulin growth factor; AKT: Protein kinase B; ATP: adenosine triphosphate; CoA: coenzyme A; IGF: insulin growth factor: mTOR: mammalian target of rapamycin: PI3K: phospatidylinositol-3-kinase; TCA: tricarboxylic acid (Sims et al., 2023).

Ketogenic diet and the Warburg effect

Cancer cells can be identified by metabolic changes that result in excessive glucose intake. This change is explained by the Warburg effect, which is defined as an increase in aerobic glycolysis for ATP production (Klement, 2019; Tan et al., 2020). Additionally, in the absence of oxygen, oxidation plays a serious role in the ATP production of cancer cells, thanks to the production of lactate from the fermentation of glucose. Apart from this, cancer cells cause excessive ROS production as a result of the electron transport system not working. Glucose, the main component of the tumor, is required for both cell survival and proliferation. Therefore, the ketogenic diet becomes a therapeutic approach by reducing the glucose level of cells and increasing the level of unused ketone bodies, which are the substrate for ATP production by cancer cells (Talib et al., 2021). While the ketogenic diet starves tumor cells, normal cells are subjected to prolonged glucose restriction, resulting in fatty acid oxidation, which plays an important role in ketone bodies synthesis. It is subsequently converted to Acetyl-CoA and enters the TCA cycle to produce ATP. In this way, ketone bodies support normal cells to stay healthy, as shown in Fig. 2 (Wallis, 2018; Tran et al., 2020; Talib et al., 2021).

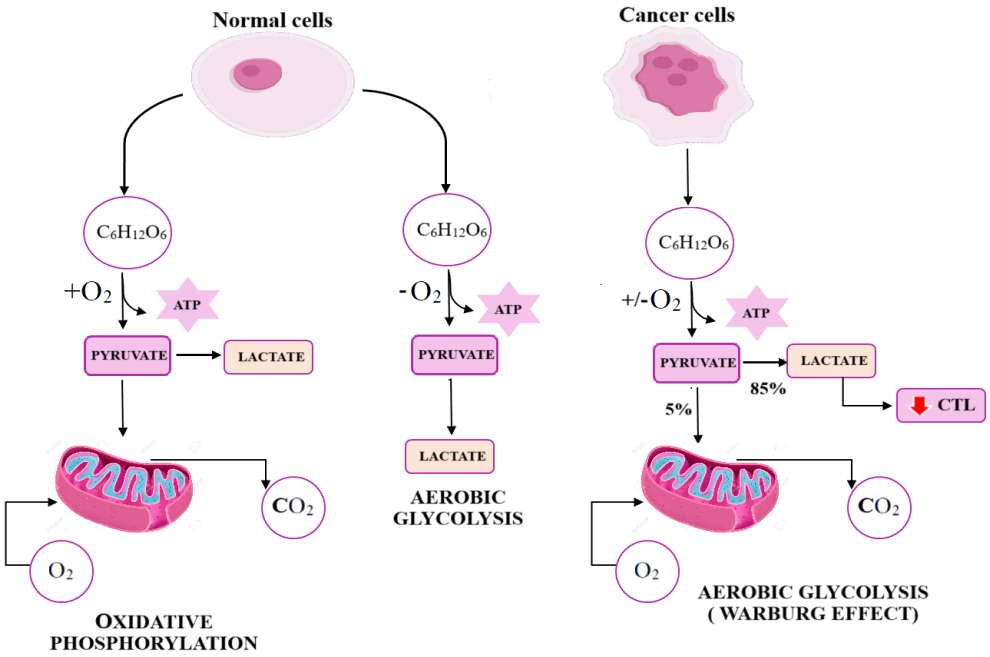

Figure 2. Warburg effect in cancer cells (Toadere et al., 2024). CTL: Cytotoxic T lymphocytes.

Preclinical and clinical studies

Poff et al, investigated the effect of a ketogenic diet in mice with systemic metastatic cancer. As a result of the study, it was determined that the ketogenic diet alone significantly reduced blood glucose, slowed tumor growth and increased the average survival time in cancerous mice by 56.7% (Poff et al., 2013). In another study, the effects of ketone bodies on pancreatic cancer were examined, and it was stated that glycolytic flux in tumor cells decreased after treatment with ketone bodies. It has been stated that ketone bodies induce apoptosis and reduce glutamine uptake, ATP content and survival in multiple pancreatic cancer cells. Ketone bodies have been found to significantly reduce cachexia in cell line models (Shukla et al., 2014). Gluschnaider et al studied mammary tumor interaction on transgenic mice. It has been stated that the ketogenic diet applied reduces tumor progression by suppressing tumor formation. This may suppress the esterification of free long-chain fatty acids into lipids due to the limiting effect of insulin and glycerol-3-phosphate, thus showing its natural tumor suppressor effect (Gluschnaider et al., 2014). The ketogenic diet has been evaluated as a new treatment in the mouse model of peritoneal dissemination of BALB/c mice. To achieve experimental peritoneal dissemination, the mouse colon adenocarcinoma cell line colon 26 was inoculated. After tumor inoculation, mice were fed a ketogenic diet, and the study showed increased survival and improved health status. It is thought that the ketogenic diet may be a preventive treatment for peritoneal spread (Kasumi and Sato, 2019). 29 patients with breast cancer who followed a ketogenic diet were compared with 30 patients who consumed their standard diet before, in the middle, and at the end of radiotherapy. Significant improvements were detected in the emotional and social functionality and sleep quality of patients following the ketogenic diet compared to those following the standard diet. Compared to the standard diet group, it was stated that the increase in breast symptoms in the ketogenic diet group was less, and metabolic health markers (such as creatinine, triglycerides) improved significantly with the ketogenic diet (Klement et al., 2021). Women (age ≥19) with ovarian and endometrial cancer experienced selective fat mass loss after 12 weeks following the ketogenic diet. It has been stated that fasting serum insulin is reduced by the ketogenic diet. It has been suggested that elevated serum β-hydroxybutyrate may create a metabolic environment unfavourable for cancer proliferation (Cohen et al., 2018).

Side effects and possible health risks of ketogenic diet

In addition to the positive effect of the ketogenic diet on weight loss, studies have shown that the diet significantly reduces serum triglycerides (Shah and Mohan, 2015). A decrease in total cholesterol and an increase in HDL (high density lipoprotein) levels have been noted. There is 3-hydroxy-3-methylglutaryl-CoA reductase enzyme, which is activated by insulin, in cholesterol biosynthesis. Thanks to this enzyme, the increase in blood glucose and subsequent insulin levels also increases the endogenous cholesterol level (Tony David et al., 2017; Shilpa and Mohan, 2018). A transient occurrence of endothelial dysfunction has been detected shortly after the start of the ketogenic diet, which may further worsen an already stressed atherosclerotic vascular system (Luong et al., 2022). Short-chain fatty acids are the products of fermentation in the intestine of indigestible foods such as dietary fiber. Thanks to lipid metabolism and glucose homeostasis, it has an improving effect on insulin sensitivity and general metabolic health.

However, since dietary fiber intake is limited during the ketogenic diet, it also reduces the production of short-chain fatty acids at the same rate (Hernández et al., 2019; Ferraris et al., 2021). The ketogenic diet also has side effects such as short-term constipation, headache, diarrhea, nausea, muscle cramps and fatigue, which are called 'keto flu' (O'Neill and Raggi, 2020). Apart from this, it has been stated that long-term effects may include hepatic steatosis, hypoproteinemia, hypocitraturia, hypercalciuria, kidney stones, risk of heart attack, vitamin and mineral deficiencies (Masood et al., 2023).

Conclusion

There is evidence that the ketogenic diet may address various health problems through different mechanisms of action. Ketogenic diet causes significant changes due to increased fatty acid oxidation and decreased glucose flux, which may be an effective mechanism for cancer treatment. The ketogenic diet can have an anti-tumor effect by targeting tumor metabolism, inflammatory process and gene transcription. From the presented studies, it has been supported that the diet provides a beneficial effect as an adjuvant treatment in mice and humans when applied together with other methods. As a result, the ketogenic diet appears to be a promising and powerful option for cancer treatment. More randomized controlled trials are needed to apply it as a standard protocol on cancer.

Conflicts of Interest

The authors declare no conflicts of interest.

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