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Süleyman Demirel Üniversitesi Sağlık Bilimleri Dergisi
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Bacak Hacmi ile Dikey Sıçrama İlişkisinin Kadın Basketbol ve Voleybolcularda İncelenmesi

Investigation of the Relationship between Leg Volume and Vertical Jump in Female Basketball and Volleyball Players

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ÖZ

Amaç: Bu çalışmanın amacı bacak hacmi ile dikey sıçrama ilişkisinin kadın basketbol ve voleybolcularda incelenmesidir. Gereç ve Yöntem: Araştırmaya 12 basketbolcu ve 12 voleybolcu olmak üzere toplam 24 kadın lisanslı sporcu gönüllü olarak katıldı. Sporculara Frustrum modeli kullanılarak toplam bacak hacmi ölçümü, cm cinsinden dikey sıçrama testi uygulanarak Lewis formülü ile watt cinsinde anaerobik güç değerine çevrildi. Verilerin analizinde tanımlayıcı istatistik; normal dağılım gösteren toplam bacak hacmi ile dikey sıçrama verileri arasındaki ilişki için "Pearson" Korelasyon Analizi kullanıldı. Anlamlılık derecesi "$p<0,05$" kabul edilerek değerlendirildi. Bulgular: Toplam bacak hacmi ve dikey sıçrama arasındaki ilişki cm cinsinde incelendiğinde iki branşta da ilişkiye rastlanmadı ($p>0,05$). Toplam bacak hacmi ve dikey sıçrama arasındaki ilişki Watt cinsinde incelendiğinde voleybolcularda ilişkiye rastlanmazken ($p>0,05$); basketbolcularda pozitif yönde anlamlı ilişkiye rastlandı ($p<0,05$). Sonuç: Sonuç olarak, çalışma bulgularına göre basketbol antrenman ve müsabaka oyununda dikey sıçrama özelliğinin voleybola nazaran daha baskın uygulanmasından kaynaklandığını düşünülmektedir. Ek olarak, basketbolda tüm oyuncuların oyun içinde ribaunt, şut, vs. gibi hareketlerde dikey sıçramayı sıklıkla kullandığı; voleybolda ise oyun içinde sadece smaç ve blok pozisyonlarında dikey sıçramanın kullanıldığından ötürü antrenörler oyun dinamiğini antrenmanlara da yansıtmaktadır. Çalışmamızın sonuçlarının bu nedenlere de dayandığını düşünmekteyiz. Ayrıca çalışmamız antrenman modeli, içeriği ve yoğunluğu belirleme açısından antrenörlere ve spor bilimcilere öneriler sunabilmektedir.

Anahtar Kelimeler: *Bacak hacmi, Dikey sıçrama, Basketbol, Voleybol*

ABSTRACT

Purpose: The purpose of study is to examine relationship between leg volume and vertical jump in female basketball and volleyball players. Materials and Methods: 24 licensed female athletes, 12 basketball players and 12 volleyball players, participated in study voluntarily. Total leg volume measurements were made using Frustrum model, vertical jump tests were applied to athletes in cm, and anaerobic power values were converted to Watts using Lewis formula. Descriptive statistics were used in analysis of data; "Pearson" Correlation Analysis was used for relationship between total leg volume and normal distribution of vertical jump data. The significance level was evaluated by accepting "$p<0.05$". Findings: When relationship between total leg volume and vertical jump was examined in cm, no relationship was found in both branches ($p>0.05$). When relationship between total leg volume and vertical jump was examined in Watts, no relationship was found in volleyball players ($p>0.05$); positive significant relationship was found in basketball players ($p<0.05$). Conclusion: As a result, it is thought that vertical jump feature is applied more dominantly in basketball training and competitive games compared to volleyball. In addition, since all players in basketball frequently use vertical jump in rebound, shot, etc. movements during game; and since vertical jump is only used in spike and block positions in volleyball, coaches also reflect game dynamics to training. We think the results of our study are based on these reasons. In addition, our study can provide suggestions to coaches and sports scientists in terms of determining training model, content and intensity.

Keywords: *Leg volume, Vertical jump, Basketball, Volleyball*

GİRİŞ

Günümüzde, sporcuların performanslarını belirleyen ve başarılarına etki eden faktörlerin incelenmesi, bu faktörlerin ne derece etkili olduğunun anlaşılması, spor bilimlerinde sporcu performansı üzerine yapılan araştırmaların başında gelmektedir (1). Spor branşlarında temel amaç, ilgili spor dalının gerektirdiği motorik özellikleri devamlı olarak geliştirmek, gelişen beceriyi yüksek seviyede korumak ve bu sayede sporcunun performansını artırmaktır (2). Bu hedefleri gerçekleştirmek için de yeni antrenman yöntemleri ve motorik becerilerin gelişimi ile ilgili yeni bağlantılar kurulmaya çalışılmaktadır (3). Sporda, gelişmiş motor beceriler (kuvvet, dayanıklılık, hız, koordinasyon, esneklik, reaksiyon hızı vb.) sporcuların performans seviyelerini belirleyen temel unsurlardır. Sporcuların başarılı olabilmesi için sağlıklı ve zinde olması, normal düzeylerin ötesinde bir fiziksel kapasiteye ulaşması ve uzun süreli, yüksek düzeyde performans gösterebilmesi başarının ön koşuludur (4). Bu unsurlar bütün spor branşları için geçerli olmaktadır.

Basketbol, voleybol, futbol, hentbol gibi top ile yapılan spor branşları, fiziksel, teknik ve taktik özellikler gerektiren kapsamlı becerilere dayanmaktadır (5). Bir spor branşında başarı yakalamak için o spor branşının gerektirdiği ve önem arz ettiği motorik becerilerin gelişmesi performansın gelişimi için oldukça önemlidir (6). Basketbol ve voleybol branşları özelinde her iki branşta da sıçrama hareketlerinin fazla sayıda yapıldığı ve performansı etkilediği için oldukça önem taşımaktadır. Basketbolda sıçrama, iyi bir kas gücü ve paylayıcı güç gerektirmektedir. Basketbolda sıçrama, savunmada çemberi korumak ve blok yapmak için oldukça önemlidir (7-9). Bunun yanı sıra hücumda şut atarken bloktan kurtulmak için, turnike atışında çembere uzanabilmek için veya blok tehlikesini minimuma düşürmek için atağı smaçla bitirmek adına sporcunun iyi bir sıçrama performansı sergilemesi ve sporcuların sıçrama becerisini geliştirmesi basketbol için önemli bir fiziksel yetenek olarak kabul edilmektedir (10). Voleybolda ise özellikle smaç ve blok unsurlarında sporcunun ne kadar yükseğe ulaşabildiği bloğun veya smacın kalitesini ve etkisini belirlediği için sıçrama becerisi oldukça önem taşımaktadır. Bunların yanı sıra smaç serviste de ulaşılan yükseklik servis performansını etkilemektedir (11). Voleybolda sporcular bu hareketleri gerçekleştirirken yapabildikleri maksimum dikey sıçramayı gerçekleştirmeleri gerekmektedir (12,13). Bu unsurlardan dolayı dikey sıçrama hem basketbolda hem de voleybolda oldukça önem taşımaktadır.

Dikey sıçrama, hız, denge ve koordinasyon gerektiren kompleks bir beceridir. Sıçrama sırasında ayakların yerle temasının kesilmesiyle başlayan hareket, uçuş evresi ve ardından yere inişle tamamlanır. Etkili bir dikey sıçrama, sıçrama yüksekliğinin yanı sıra hızla ağırlık merkezinin stabilitesine bağlıdır. Ayrıca, itme anında ayaklar ve vücudun dikey eksende dengede kalması, kas aktivasyonuyla doğrudan ilişkilidir. Sıçramanın başlangıç fazında, kişinin ağırlık merkezi destek noktasına hizalı olmalıdır ki, etkili bir itme gerçekleştirilebilsin (14). Dikey sıçrama performansı hem kas gücü hem de sinirsel mekanizmalar tarafından belirlenir. Yerden en yüksek noktaya sıçrayabilmek için, yerle temas kesilmeden önce maksimum dikey ivme sağlanmalıdır. Bu ivme, sporcuya başlangıçta en büyük dikey hızı kazandırır. Başlangıç hızı ne kadar yüksek olursa, vücut kütlesi de o kadar yukarıya taşınır. En yüksek dikey ivmeyi elde etmek için, sporcu mümkün olan en kısa sürede maksimum gücü üretmelidir. Kas kütlesini artırmak ve nöral mekanizmaları, örneğin kas iğciği germe refleksini hızlandırarak, sporcu daha hızlı tepki verebilir ve daha yükseğe sıçrayabilir (12,13). Dikey sıçramayı etkileyen faktörlerden birinin de bacak hacmi olduğu düşünülmektedir. Bacak hacmi, kasın ortaya çıkardığı gücü ve kuvveti arttırabildiği için sporcunun performansını belirleyen faktörler arasında bulunmaktadır (15). Bacak hacminin oluşturulan gücü ve kuvveti etkilemesinin sebebi o bölgede kas liflerinin sayısının artması ve kasın enerji depolama kapasitesinde artış meydana gelmesidir (16). Bu artışın dikey sıçramayı ne kadar etkilediği merak konusudur.

Bu bilgiler doğrultusunda araştırmamızın amacı bacak hacmi ile dikey sıçrama ilişkisinin kadın basketbol ve voleybolcularda incelenmesidir.

GEREÇ ve YÖNTEM

Araştırmanın Evren ve Örneklemi

Araştırmaya 12 voleybolcu ve 12 basketbolcu toplam 24 kadın lisanslı sporcu "Bilgilendirilmiş Gönüllü Olur Formu" doldurtularak katıldı. Ek olarak, sporculara verilerin gizliliği hususunda bilgilendirme yapıldı.

Araştırmanın Sınırlılıkları

Araştırma bir basketbol (n=12) ve bir voleybol (n=12) lisanslı kadın takımı ile sınırlandırılmıştır.

Veri Toplama Araçları

Bacak Hacmi Ölçümü

Sporcuların bacak hacmi, uyluk, baldır ve ayak hacimlerinin toplamı olarak hesaplandı. Uyluk hacmi, kasık bölgesindeki katlantı ile tibial nokta arasındaki mesafeye göre, baldır hacmi ise tibial nokta ile iç ayak kemiği noktası arasındaki mesafeye göre ölçüldü. Ayak hacmi ise iç ayak kemiği ile ayak uç noktası arasındaki mesafe dikkate alınarak hesaplandı. Bu mesafeler, %10'luk aralıklarla belirlendi ve Frustum işaret model yöntemi kullanılarak mezura ile ölçüldü (17-22).

Dikey Sıçrama Ölçümü

Sporculara 5-99 cm arasında ölçüm kapasitesine sahip mesafeyi dijital olarak gösteren Takei marka jump metre kullanılarak serbest dikey sıçrama testi uygulandı. En iyi sonuç "cm" olarak kaydedildi. Ayrıca dikey sıçrama verileri "Lewis" formülü kullanılarak "Watt" olarak hesaplandı.

Lewis Formülü: Güç (Watts) = √ 4.9 x vücut ağırlığı (kg) x √ sıçrama mesafesi (m) x 9.81

Çalışmanın Etik Yönü

Çalışmaya başlamadan önce Süleyman Demirel Üniversitesi Sağlık Bilimleri Etik Kurulu'nun 06.01.2025 tarihli ve 88/11 sayılı kararı ile etik izin alınmıştır.

Verilerin Analizi

Veriler SPSS 22.0 istatistik paket programı kullanılarak analiz edildi. Demografik bilgiler için tanımlayıcı istatistik; toplam bacak hacmi ve dikey sıçrama verilerinin normallik testi için "Shapiro-Wilk"; verilerinin normal dağılım gösterdiğinin tespiti üzerine ilişki testi için "Pearson" Korelasyon Analizi kullanıldı. Önem derecesi "$p<0,05$" kabul edilerek değerlendirildi.

BULGULAR

Tablo 1'e göre; basketbolcuların yaş ortalaması 21,16±2,16 yıl, voleybolcuların ise 21,41±1,24 yıldır. Boy ortalaması basketbolcular için 169,75±6,55 cm, voleybolcular için 168,91±6,50 cm olarak belirlendi. Vücut ağırlığı ortalaması basketbolcularda 58,12±5,84 kg, voleybolcularda 59,83±5,67 kg'dı. Ayrıca, beden kitle indeksi ortalaması basketbolcularda 20,02±1,53 kg/m², voleybolcularda ise 24,20±3,54 kg/m² olarak saptandı.

Tablo 1: Sporcuların Demografik Bilgileri

		Yaş (yıl)	Boy (cm)	Vücut Ağırlığı (kg)	BKİ (kg/m²)
Branş	**n**	**Ort±SS**	**Ort±SS**	**Ort±SS**	**Ort±SS**
Basketbol	12	21,16±2,16	169,75±6,55	58,12±5,84	20,02±1,53
Voleybol	12	21,41±1,24	168,91±6,50	59,83±5,67	24,20±3,54

Tablo 2 incelendiğinde, toplam bacak hacmi basketbolcularda 8921,35±1234,78, voleybolcularda 17980,40±1578,66 lt; dikey sıçrama performansı (cm cinsinden) basketbolcularda 24,43±3,50, voleybolcularda 28,29±3,50 cm olarak hesaplandı. Toplam bacak hacmi ile dikey sıçrama arasında basketbol (r=,079; p=,808) ve voleybolda (r=,011; p=,973) anlamlı bir ilişki bulunamadı (p>0,05).

Tablo 2: Sporcuların Toplam Bacak Hacmi (lt) ve Dikey Sıçrama (cm) İlişkisi

	Toplam Bacak Hacmi (lt)	**Dikey Sıçrama (cm)**		
Branş	**Ort±SS**	**Ort±SS**	**r**	**p**
Basketbol	8921,35±1234,78	24,43±3,50	,079	,808
Voleybol	17980,40±1578,66	28,29±3,50	,011	,973

* Pearson Korelasyon Analizi kullanıldı.

Tablo 3'e göre, toplam bacak hacmi basketbolcularda 8921,35±1234,78, voleybolcularda 17980,40±1578,66 lt; dikey sıçrama performansı (Watt cinsinden) basketbolcularda 1959,03±237,36, voleybolcularda 2177,53±234,91 Watt olarak hesaplandı. Toplam bacak hacmi ile dikey sıçrama arasında basketbolda (r=,701; p=,011) pozitif yönlü anlamlı ilişki varken (p<0,05); voleybolda (r=,154; p=,633) anlamlı bir ilişki bulunamadı (p>0,05).

Tablo 3: Sporcuların Toplam Bacak Hacmi (lt) ve Dikey Sıçrama (Watt) İlişkisi

	Toplam Bacak Hacmi (lt)	**Dikey Sıçrama (Watt)**		
Branş	**Ort±SS**	**Ort±SS**	**r**	**p**
Basketbol	8921,35±1234,78	1959,03±237,36	,701	,011
Voleybol	17980,40±1578,66	2177,53±234,91	,154	,633

* Pearson Korelasyon Analizi kullanıldı.

TARTIŞMA

Dikey sıçrama, sporcunun atletik performansının değerlendirilmesi, kişinin sportif anlamda güçlü ve zayıf yönlerini tespit edilmesi gibi konularda kullanılmaktadır (23). Dikey sıçrama bize alt ekstremitede anaerobik güç kapasitesi hakkında da bilgi vermektedir (24,25). Basketbol ve voleybol branşlarında çok sayıda sıçrama gerçekleştirildiği için sıçrama becerisi ve bu beceriyi etkileyen faktörler oldukça önem taşımaktadır (25-27). Bu branşlarda sıçrama sayısının fazla olması ve smaç, blok gibi hem savunma hem de hücumu doğrudan etkileyen tekniklerde kullanılması açısından dikey sıçrama bu branşlarda sporcunun atletik performansını değerlendirirken belirleyici faktör olarak kabul edilmektedir (28,29). Bu doğrultuda çalışmamızda bacak hacmi ile dikey sıçrama ilişkisi kadın basketbol ve voleybolcularda incelenmiştir.

Çalışmamızda, kadın basketbolcularda toplam bacak hacmi ile dikey sıçrama performansının watt cinsinden verileri arasında pozitif yönlü anlamlı bir ilişki bulunurken, kadın voleybolcularda toplam bacak hacmi ile dikey sıçrama arasında bir ilişkiye rastlanmamıştır. Bunun nedeni olarak basketbol antrenman ve müsabaka karakteristiğinde voleybola nazaran dikey sıçrama özelliğinin daha sık ve yoğun kullanıldığından kaynaklandığını düşünmekteyiz.

Bacak hacminin dikey sıçramaya olan etkisinin araştırıldığı bazı çalışmalar yapılmıştır. Erkek futbolcular üzerine yapılan çalışmada quadriceps oranı ve dikey sıçrama performansı arasında pozitif yönlü anlamlı bir ilişki bulmuştur (30). Bacak hacmi, kas kesit alanı, kas kütlesi ve kasın fibril uzunluğu üretilen anaerobik gücü ve gerçekleştirilen dikey sıçramayı etkileyen faktörler arasındadır ve yapılan araştırmalarda bu parametrelerin fazla olduğu deneklerin anaerobik güç ve dikey sıçrama performansının daha iyi olduğu ifade edilmektedir (31). Yapılan bir diğer araştırmada bacak hacminin, kas kütlesi ve kas lif sayısından meydana gelmesi ve bu unsurların fazlalığı, üretilen kuvvet ile doğru orantılı olduğu bu yüzden de bacak hacmi ile dikey sıçrama performansı arasında anlamlı bir ilişki bulunduğu ifade edilmiştir (32-34). Basketbolcu ve voleybolcularda yapılan bir başka çalışmada ise dikey sıçrama ölçülerine bakıldığında basketbolcular lehine anlamlı bir fark tespit edilmiştir ve bunun sebebi olarak da basketbolcuların antrenmanda sıçrama becerisini daha yoğun kullandığı ifade edilmiştir (35). De Ste Croix ve ark. (2000) tarafından yapılan çalışmada ise bacak hacmi ile birlikte vücut ağırlığının, deri kıvrım kalınlığının, yaşın, cinsiyetin ve izokinetik bacak kuvvetinin dikey sıçrama ve anaerobik performans değerleri üzerindeki etkisi incelenmiştir. Çalışmada artan bacak kas hacminin dikey sıçrama ve anaerobik performans değerleri üzerinde anlamlı bir etkisinin olduğu ifade edilmiştir (36). Voleybolcularda yapılan bir çalışmada ise artan bacak hacminin dikey sıçramayı olumlu yönde etkilediği bulunmuştur (37).

Voleybolcularda yapılan bazı çalışmalarda bizim çalışmamızla aynı sonuç bulunmuştur. Yapılan çalışmada genç voleybolcularda bacak hacmi, uyluk kütlesi, baldır kütlesi ve ayak kütlesi ile dikey sıçrama arasında anlamlı bir ilişki bulunamamıştır (38). Diğer branşlarda da bu sonuca yakın sonuçlar bulunmuştur. Apaydın (2020), kadın futbolcularda yaptığı çalışmada alt ekstremite kuvvet değişkenlerinin dikey sıçrama ile anlamlı bir ilişki olmadığını ifade etmiştir (39).

Dikey sıçrama özelliğinin bir anaerobik güç çıktısı olduğu düşünüldüğünde bazı araştırmacılar toplam bacak hacmi ve maksimal kuvvet ilişkisini incelemiş ve pozitif yönde anlamlı ilişkiler tespit etmiştir (40). Işıldak yapmış olduğu çalışmalarda toplam bacak hacmi ve anaerobik güç arasındaki ilişkide pozitif yönde etkiler olduğunu ileri sürmüş, nedeni olarak da yapılan antrenmanların etkisine dikkat çekmişlerdir (41,42). Özkan ve Sarol yaptığı bir çalışmada bacak hacmi ile anaerobik güç arasında anlamlı bir ilişki bulmuş ve bu ilişkinin anaerobik performansı olumlu yönde etkilediğini belirtirken, bacak kütlesi ile bacak kuvveti arasında anlamlı bir ilişki bulunamadığını ifade etmişlerdir (43). Bir diğer çalışmada ise bacak hacmi, kas kütlesi, kas fibril uzunluğu ve kas kesit alanının anaerobik ortamda kasın üreteceği gücü etkileyen unsurlar olduğu ifade edilmiştir (44). Çocuklarda yapılan bir çalışmada aynı sporcularda olduğu gibi çocuklarda da bacak hacminin anaerobik güce etkisinin olduğu belirtilmiştir (45). Çocuklarda yapılan bir diğer çalışmada bacak hacminin yanı sıra kas kitlesi ve kas kesit alanının da anaerobik güç ve performans üzerinde etkili olduğu ifade edilmiştir (46). Son olarak Özkan ve diğerlerinin yaptığı çalışmada da bacak hacmi ve kütlesi ile anaerobik güç ve performans arasında anlamlı bir ilişki olduğu ve bu ilişkinin sebebinin kas kesit alanının artışı ile bu sayede ATP-PC depolarının da artışına bağlı olduğu bunun yanı sıra kas kitlesinin büyüklüğü üretilen güç ile doğru orantılı olduğunu fakat kasın fibril yapısının da üretilen gücü etkileyebileceği belirtilmiştir (47).

SONUÇ

Sonuç olarak, çalışmamızda toplam bacak hacmi ile dikey sıçrama ilişkisinde basketbolcularda pozitif yönde anlamlı ilişkiye rastlanırken; voleybolcularda ilişkiye rastlanmamıştır. Bunun sebebi basketbol antrenman ve müsabaka oyununda dikey sıçrama özelliğinin voleybola nazaran daha baskın uygulanmasından kaynaklandığını düşünmekteyiz. Ek olarak, basketbolda tüm oyuncuların oyun içinde ribaunt, şut, vs. gibi hareketlerde dikey sıçramayı sıklıkla kullandığı; voleybolda ise oyun içinde sadece smaç ve blok pozisyonlarında dikey sıçramanın kullanıldığı bilinmektedir. Bu yüzden iki branşında antrenörleri oyun dinamiğini antrenmanlara da yansıtmaktadır. Çalışmamızın sonuçlarının bu nedenlere de dayandığını düşünmekteyiz. Ayrıca çalışmamız antrenman modeli, içeriği ve yoğunluğu belirleme açısından antrenörlere ve spor bilimcilere öneriler sunabilmektedir.

Sınırlılıklar: Çalışma sadece kadın basketbol ve voleybolcular ile sınırlandırılmıştır. İleride yapılacak olan çalışmalarda cinsiyet farklılığı ve branş değişikliği gözetilerek bacak hacmi ve dikey sıçrama arasındaki ilişki vurgulanabilir.
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Yazarlık Katkısı: Makalenin tasarımı: SD, MA; Makale verilerinin elde edilmesi: SD; Verilerin analiz edilmesi: SD, MA; Makale taslağının oluşturulması: SD, MA; İçerik için eleştirel gözden geçirme: SD, MA; Yayınlanacak versiyonun son onayı: SD, MA.

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Post Endodontik Restorasyonlarda Kullanılan Post-Kor Sistemlerinin Kırılma Dayanımı Karşılaştırması

Comparasion of Fracture Strength of Post-Core Systems used in Post-Endodontic Restorations

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ÖZ

Amaç: Bu çalışma ile fazla madde kaybına uğramış endodontik tedavili dişlerin restorasyonunda kullanılan farklı post-kor sistemlerini kırılma dayanımları açısından karşılaştırmak amaçlanmıştır. Gereç ve Yöntem: Çalışmada çekilmiş, tek köklü, tek kanallı 45 adet kronu uzaklaştırılmış insan alt premolar dişi kullanıldı. Dişlere kök kanal tedavisi uygulandıktan sonra kök kanallarına post yuvası açıldı. Dişler 3 gruba ayrılarak Grup 1'e cam fiber post-kompozit kor, Grup 2'ye kompozit post-kor, Grup 3'e ise lityum disilikat post-kor hazırlandı. Daha sonra dişlere universal test cihazında kuvvet uygulanarak kırılma dayanımı değerleri tespit edildi ve dişlerde oluşan kırık tipleri incelendi. Verilerin istatistiksel analizinde Bonferroni ve Shapiro-Wilk testleri kullanılarak, sonuçlar değerlendirildi. Bulgular: Elde edilen sonuçların istatistiksel değerlendirmesi sonucunda grupların kırılma dayanımı değerleri arasında istatistiksel olarak anlamlı bir farklılık tespit edildi ($p<0,05$). Fiber post-kompozit kor grubundaki dişlerin kırılma dayanımı, diğer iki gruptan anlamlı derecede düşük bulunmuşken, kompozit post-kor ve lityum disilikat post-kor grupları arasında kırılma dayanımı açısından fark bulunmamıştır. Fiber post-kompozit kor grubunda restore edilebilir kırık tipi, kompozit post-kor ve lityum disilikat post-kor gruplarında ise restore edilemez kırık tipleri daha fazla görüldü. Sonuç: Bu çalışmanın sınırları dahilinde, kısa post uygulamalarında, fiber post-kompozit kor grubunun kırılma dayanımının, kompozit post-kor ve lityum disilikat post-kor gruplarına göre daha düşük olduğu tespit edilmiştir. Ayrıca fiber post- kompozit kor grubundaki kırık tiplerinin daha restore edilebilir olduğu gözlendi. Yeterli ferrule desteği bulunmayan, çok fazla madde kaybı olan premolar dişlerin restorasyonunda monoblok şekilde uygulanan post-kor sistemlerinin tercih edilmesiyle daha yüksek kuvvetlere dayanıklı restorasyonlar elde edilebilir.

Anahtar Kelimeler: *Fiber post, Kırılma dayanımı, Post-kor*

ABSTRACT

Objective: The aim of this study was to compare the fracture strength of different post-core systems used in the restoration of endodontically treated teeth with excessive material loss. Materials and Methods: Forty-five single and straight-root decoronated human mandibular premolar teeth were used. After root canal treatment, post space preparation have been made. Teeth were randomly divided into three groups : Group 1 glass fiber post-composite core, Group 2 composite post-core, Group 3 lithium disilicate post-core.For all groups, fracture resistance (N) value was measured and recorded using a universal testing machine. The types of fractures in the teeth were examined. Bonferroni and Shapiro-Wilk tests were used for statistical analysis of the data. Results: As a result of the statistical evaluation of the results obtained, a statistically significant difference was found between the fracture strength values of the groups ($p<0.05$). The fracture strength of the teeth in the fiber post-composite core group was significantly lower than the other two groups, while there was no significant difference in fracture strength between the composite post-core and lithium disilicate post-core groups. Restorable fracture types were more common in the fiber post-composite core group, while unrestorable fracture types were more common in the composite post-core and lithium disilicate post-core groups. Conclusion: Within the limitations of this study, in short post applications, the fracture strength of the fiber post-composite core group was lower than the composite post-core and lithium disilicate post-core groups, and the fracture types in the fiber post-composite core group were more restorable. Restorations resistant to higher forces can be achieved by choosing monoblock post-core systems in the restoration of premolar teeth that do not have sufficient ferrule support and have too much substance loss.

Keywords: *Fiber post, Fracture resistance, Post-core*

GİRİŞ

Endodontik tedavi görmüş, fazla madde kaybına sahip dişlerin restorasyonu diş hekimleri için her zaman zorlu ve komplike olmuştur. Endodonti alanındaki yeni gelişmeler, materyaller ve yöntemlerle geçmişte çekim endikasyonu konulan dişlerin, günümüzde tedavi başarısı ve ağızdaki sağ kalım oranı artmıştır. Kök kanal tedavisi uygulanmış, koronal harabiyeti çok fazla olan dişlerde diş çekimi artık yerini kök kanalından destek alınan bir yöntem olan post-kor restorasyon uygulamalarına bırakmıştır (1).

Post; kök kanalının 2/3 kısmına kadar uzanan, destek ve retansiyonu sağlayan bölümdür. İdeal bir post, dişlere zarar vermeden gerekli retansiyonu sağlar (1). Post, dişi direkt olarak güçlendirmez veya kalan dentin dokusunun kırılmaya karşı direncini artırmaz. Kor; postun koronal uzantısı olarak düşünülebilir. Prepare edilmiş diş formunda, restorasyonu post ile birleştiren kron kısmıdır. Korun birincil amacı, restorasyonun dayanıklılığını artırmak ve restorasyona gelen kuvvetleri alt diş yapısına uygun şekilde dağıtmaktır (2).

Günümüzde elastisite modülü dentinden çok yüksek olan metal postlar yerine dentine benzer elastisite modülüne sahip fiber postların kullanım sıklığı artmıştır (3). Fiber postlar, pasif olarak yerleştirilir ve dentin yüzeyine adeziv rezin simanlar aracılığı ile tutunurlar (4). Fiber postlar; uygulanma kolaylığı, avantaj sağlayan fiziksel ve mekanik özellikleri, gerektiğinde kanaldan uzaklaştırılmalarının kolay olması ile estetik özellikleri nedeniyle günümüzde sıklıkla kullanılan materyaller olma özelliklerini korumaktadır.

Kırık oluşumu riskini en aza indirmek için fiber postlarla birlikte kompozit rezin siman ve kor materyali kullanılabilir (5,6). Monoblok yapıyı oluşturan materyallerin (dentin, post, siman, kor vb.) benzer elastisite modülüne sahip olması gerekir (5). Yüksek elastisite modülüne sahip postların yükleme sırasında dişleriyle birlikte bükülmemesi nedeniyle kırıklar meydana gelir.

CAD/CAM teknolojisi ile seramik ve seramik benzeri materyallerin gelişimi yüksek kaliteli restoratif dental tedavilerin gerçekleştirilmesine olanak sağladı (7,8). Dijital diş hekimliğindeki gelişmeler ile lösit ile.güçlendirilmiş cam.seramik, lityum disilikat.cam-seramik, hibrit polimer seramik gibi yüksek performanslı materyallerin kullanımı restoratif diş hekimliği tedavilerinde önemli alan kapladı (7). Seramik materyallerindeki bu gelişmeler ve çeşitlilik sayesinde seramik post-kor sistemleri yeni bir method olarak klinik rutinine girdi. Lityum disilikat cam seramikleri, kron restorasyon malzemeleri olarak yaygın olarak kullanılmaya başlanmıştır. Cam seramikler yüksek stabiliteye, biyouyumluluğa ve kolay çalışabilirliğe sahip olduklarından, uzun süreli stabilite gerektiren restorasyonlar için uygundur (9). Ek olarak, lityum disilikat cam seramiklerin endodontik tedavi görmüş dişlere post-kor olarak uygulanma sıklığı artmıştır.

Bu çalışma, metal içermeyen 3 farklı post-kor restorasyonu ile restore edilmiş, fazla miktarda koronal harabiyete sahip olan kök kanal tedavili dişlerin kırılma direncini ve tipini değerlendirmeyi amaçlanmaktadır. Bu çalışmanın H0 hipotezi; farklı post-kor sistemlerinin dişlere uygulanması sonrası kırılma dayanımları arasında fark yoktur. H1 hipotezi; farklı post-kor sistemlerinin dişlere uygulanması sonrası kırılma dayanımları arasında farklılıklar vardır.

GEREÇ ve YÖNTEM

Çalışmanın güç analizi GPower 3.1.9.2.(universitaet Kiel, Germany) programı ile gerçekleştirildi. Etki büyüklüğü 0,638 olarak hesaplandı. Güç değeri %95 ve hata payı 0,05 için her bir post-kor grubunda n=15 alınması planlanarak toplam 45 diş için çalışmanın tamamlanmasına karar verildi. Her bir post-kor grubu için n=15 alınması planlanarak toplam 45 diş ile çalışmanın tamamlanmasına karar verildi. Periodontal ve ortodontik nedenlerle çekilmiş, kök ucu gelişimini tamamlamış, aynı kök uzunluğuna sahip tek köklü ve tek kanallı, labio-lingual ve mezio-distal boyutları aynı (±0.2) 45 adet alt küçük azı dişi toplandı. Seçilen dişler işlem öncesi % 0,5'lik sodyum hipoklorit

çözeltisiyle dezenfekte edilmesinin ardından distile su ile bolca yıkanıp distile su (Sigma Aldrich, St. Louis, Missouri, Amerika Birleşik Devletleri) ile dolu koyu renkli, kapaklı cam kaplarda bekletildi. Dişlerin geride kalan kök boyları radyografik apeksten itibaren 13 mm olacak şekilde dekronize edildi.

Çalışma boyları dental operasyon mikroskobu altında 10 numaralı K tipi kanal eğesinin apikal foramene ulaştığı noktadan 1 mm kısa olacak şekilde belirlendi. Tek bir operatör tarafından üretici firmanın talimatları doğrultusunda kök kanal preparasyonu yapıldı. Kök kanal tedavisi tüm dişlerde; çalışma uzunluğunda EdgeFile X3 eğe sisteminin (Edge Endo, Albuquerque, New Mexico, Amerika Birleşik Devletleri) C1 (20/0,06), C2 (25/0,06) ve C3 (30/0,06) eğeleri X-Smart Plus (Dentsply, Maillefer, Ballaigues, İsviçre) endodontik motoru ile "Rotasyon" modunda 350 rpm hız ve 3 N/cm tork değerlerinde ile kullanıldı.

Tüm çalışma boyunca yapılan her farklı irrigasyon işlemi için tek kullanımlık 2 ml'lik 27 gauge perfore enjektör (Genject A.Ş., Ankara, Türkiye) kullanıldı. Kök kanal şekillendirmesi tamamlandıktan sonra 2 ml %5 NaOCl (MICROVEM, Altun Medikal, Sakarya, Türkiye) ile irrigasyon yapıldı. Ardından 2 ml steril izotonik serum fizyolojik (TURKTIPSAN Sağlık Turizm Eğitim ve Tic. A.Ş., Ankara, Türkiye) irrigasyonu ile kanallardaki fazla NaOCL uzaklaştırıldı. Sonrasında; smear tabakasını uzaklaştırmak için 2 ml %17'lik EDTA solüsyonu (WERAX, Spot Dental, İzmir, Türkiye) ile irrigasyon yapıldı. Ardından 2 ml steril izotonik serum fizyolojik irrigasyonu ile kanallardaki fazla EDTA uzaklaştırıldı.

Kanallar 30/0,06 guta perka konu (PearlEndo, Ho Chi Minh, Vietnam)ile kanal patına (AH Plus; DeTrey Dentsply, Kontanz, Germany) bulanarak kök kanalına yerleştirildi.

Bütün gruplardaki preparasyonların standardizasyonunun sağlanması için post boşluğunun uzunluğu 5 mm olacak şekilde bir stopper yardımı ile drillin üzerine işaretlendi. Kanaldaki guta perka 2 numaralı postun kalibre edilmiş paslanmaz çelik drilli (Angelus, Londrina, Parana, Brezilya) kullanılarak uzaklaştırıldı.

Deney grupları için toplam 45 adet diş rastgele 3 gruba ayrıldı. 1. gruba 2 numara Reforpost cam fiber post (Cam fiber, Angelus, Londrina, Parana, Brezilya), 2. gruba kompozit (GC,Gradia Core, Tokyo, Japonya) post-kor,3. gruba lityum disilikat (Upcera,Shenzhen Upcera Dental Technology,China) post-kor uygulanmıştır.

Tablo 1: Deney Gruplarının Sınıflandırılması

GRUP	POST	KOR
F	Fiber	Kompozit
K	Kompozit	Kompozit
L	Lityum disilikat	Lityum disilikat

Fiber post yerleştirilecek grupta postun dezenfeksiyonunu sağlayabilmek amacıyla cam godenin (Imıcryl, Konya, Türkiye) içine %96'lık etil alkol (Vın.s Industries, Bourgas, Bulgaristan) konularak yapıştırılana kadar minimum 1 dakika olacak şekilde alkol içerisinde bekletildi. Kök kanalları post boşluğunu dezenfekte edebilmek için 27 gauge perfore enjektör ile %17'lik EDTA (WERAX, Spot Dental, İzmir, Türkiye) ardından %5'lik NaOCl (MICROVEM, Altun Medikal, Sakarya, Türkiye) ile yıkanıp en son serum fizyolojik (TURKTIPSAN Sağlık Turizm Eğitim ve Tic. A.Ş., Ankara, Türkiye) ile irrigasyon yapıldı.

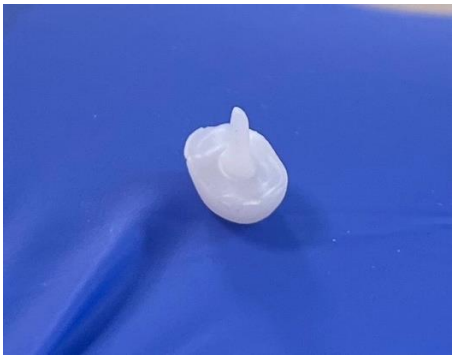
Daha sonra endodontik uç (GC, Tokyo, Japonya) ile Gradia Core dual cured kompozit (GC, Tokyo, Japonya) doğrudan post boşluğuna sıkıldı ve post boşluğu apikalden koronale doğru dolduruldu.

Fiber postlar kanal içerisine parmak basıncı ile yerleştirildi ve 20 sn LED ışık kaynağıyla (Stern Weber, T-LED S200, Imola, İtalya) polimerize edilerek sonrasında 4 dakika beklendi. Postların simantasyon işlemleri tamamlandıktan sonra Gradia Core dual cured kompozit (GC, Tokyo, Japonya) ile kuronal korlar yapılmıştır.

Kompozit post-kor grubunda endodontik uç (GC, Tokyo, Japonya) ile Gradia Core dual cured kompozit (GC, Tokyo, Japonya) doğrudan post boşluğuna sıkıldı ve post boşluğu apikalden koronale doğru dolduruldu. Kor yapımı inkremental teknik ile her tabakası 1,5 mm yüksekliğinde olacak şekilde 3 tabaka (4,5 mm yüksekliğinde) olarak yerleştirildi ve her tabaka 5 saniye süre ile LED ışık kaynağıyla polimerize edildi. Final ışınlama üretici talimatlarına göre 20 saniye süre ile yapıldı.

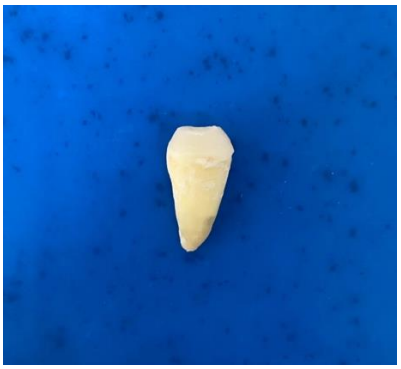
Lityum disilikat post-kor grubu için hazırlanan preparasyon boşluklarının digital ölçüsü VIRTUO VIVO™ intraoral tarayıcı (Straumann,Canada) ile alındı. Alınan ölçülerden labarotuarda sulu kesim ile TwinMac T40(Turkuaz Dental) kazıma cihazında 15 dakika sürede lityum-disilikat bloktan (Upcera,Shenzhen Upcera Dental Technology,China) monoblok post-kor elde edildi.

Şekil 1: Lityum Disilikat Post-Kor Grubu İçin Post Yuvası Ölçüsünün Ağız İçi Tarayıcı Ile Alınması



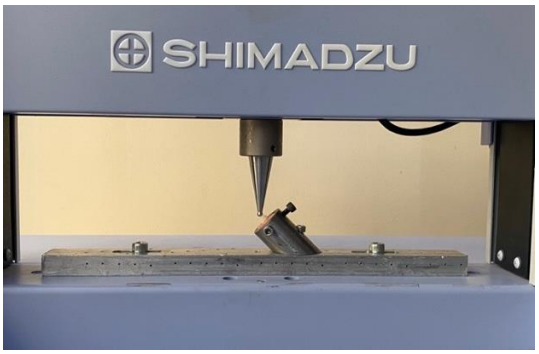
Şekil 2: Elde Edilen Lityum Disilikat Post-Kor

Lityum-disilikat post-korların yüzeyine %9.5'lik HF asit (BISCO,Porcelen Etchant Schaumburg, USA) ardından, silan (G-Multi Primer, GC, Tokyo, Japonya) uygulandı. G-Premio universal bond (GC, Tokyo, Japonya) uygulaması sonrası endodontik uç (GC, Tokyo, Japonya) ile G-Cem one (GC, Tokyo, Japonya) self-adeziv dual cure rezin siman seramik yüzeyine sıkıldı ve lityum disilikat post-korlar dişe parmak basıncı ile yapıştırılıp simante edildi.



Şekil 3: Simante Edilmiş Lityum Disilikat Post-Kor

Tüm dişler akrilik rezin blok (Imıcryl, Konya, Türkiye) içine mine-sement sınırının 2 mm altına kadar gömüldü. Örnekler universal test cihazına (AG-50, Shimadzu, Japonya) bağlandı. Akrilik bloklar silindirik uç dişin ve postun uzun eksenlerine 45° açıyla bukkal kasptan kuvvet uygulayacak şekilde yerleştirildi. 5 mm çapındaki metal uç ile 0,5 mm/dk'lık hız ile dişte kırık oluşana kadar kuvvet uygulandı. Maksimum mukavement değerleri Newton cinsinden kaydedildi, veriler toplandı ve dişlerde oluşan kırık tipleri incelendi.



Şekil 4: Universal Test Cihazı (AG-50, Shimadzu, Japonya) Ve Test Cihazına Yerleştirilen Akrilik Bloğa Kuvvet Uygulanması

Çalışmada kırılma dayanımı testi sonucunda elde edilen veriler SPSS 25.0 (Statistical Package for Social Sciences) programına aktarılarak istatistiksel analizlerle değerlendirilmiştir. İstatistiksel analizlere geçmeden önce veri giriş hatasının olmaması ve parametrelerin beklenen aralıkta olup olmadığı ile ilgili kontroller yapılmıştır. İstatistiksel anlamlılık düzeyi olarak $p<0,05$ olarak belirlenmiştir. Çalışmada öncelikle dağılımın normalliği Shapiro-Wilk testi ile kontrol edilmiştir. Elde edilen sonuçlara göre p değeri 0,05'in bulunup dağılımın normalliği kabul edilerek parametrik test yapılması uygun bulunmuştur. Tüm gruplardaki kırılma dayanımı verileri tek yönlü varyans analizi (ANOVA) ile değerlendirilmiştir. Tek yönlü varyans analizi testinde anlamlı çıkan sonuçlarda ikili grup karşılaştırması gerçekleştirmek üzere Bonferroni testinden yararlanılmıştır.

BULGULAR

Bu tez çalışmasına toplamda 45 adet çekilmiş alt premolar dişi dahil edilmiş olup, bu dişler hazırlanan post-kor sistemlerine 3 gruba ayrılmıştır.Grup 1'de cam fiber post(Reforpost)-kompozit kor(GC,Gradia Core, Tokyo, Japonya), 2. gruba kompozit (GC,Gradia Core, Tokyo, Japonya) post-kor,3. gruba lityum disilikat (Upcera,Shenzhen Upcera Dental Technology ,China) post-kor uygulanmıştır.

Çalışma kapsamında uygulanan kırılma dayanımı testi sonucunda elde edilen maksimum kuvvet verilerinin grup ortalamaları arasında istatistiksel olarak anlamlı farklılık olup olmadığı Varyans analizi ANOVA ile test edilmiştir. Analiz sonucuna göre grupların maksimum kuvvetlerinin ortalamaları arasında istatistiksel olarak anlamlı farklılık olduğu tespit edilmiştir ($p=0,000<0,05$) (Tablo 3).

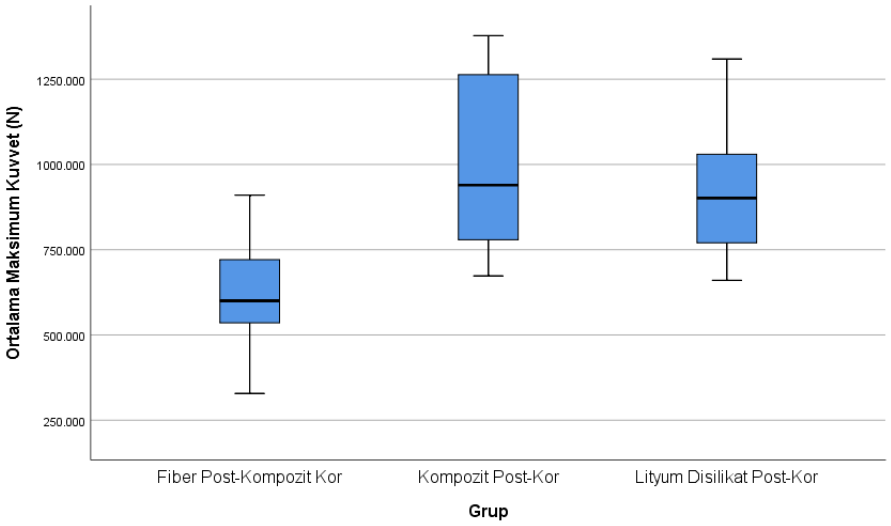
Farklılığın hangi iki grup arasında olduğunu tespit edebilmek için Bonferroni analizi yapılmıştır. Analiz sonuçları tabloda verilmektedir.

Tablo 2: Gruplara Göre Maksimum Kuvvetin Karşılaştırılması

	n	Min	Medyan	Maksimum	Ort±Ss	F	p
F	15	328,384	600,144	910,088	615,934±152,850	17,750	0,000*
K	15	673,022	939,283	1377,600	1005,305±258,363		
L	15	660,108	901,272	1309,380	926,402±204,364		
Toplam	45	328,384	800,810	1377,600	849,214±266,178		

*F: Varyans Analizi ANOVA Test istatistiği, *p<0,05, Ort: Ortalama, Ss: Standart sapma*

Analiz sonucuna göre farklılığın F grubundan kaynaklandığı tespit edilmiştir. Buna göre F grubunun maksimum kuvvet ortalama değeri 615,934±152,850, K grubunun ortalama 1005,305±258,363 (p=0,000<0,05) ve L grubunun ortalama 926,402±204,364 (p=0,001<0,05) değerlerine göre daha az olduğu görülmektedir. K grubunun ortalama 1005,305±258,363 ve L grubunun ortalama 926,402±204,364 değerleri arasında istatistiksel olarak anlamlı farklılık olmadığı tespit edilmiştir (p=0,926>0,05).



Grafik 1: Kırılma Dayanımı Değerlerinin (Ortalama Maksimum Kuvvet) Gruplara Göre Karşılaştırılması

Kor ile birlikte kök kırığı oluşan dişler tamir edilemez (katastrofik) kırık olarak, kök kırığı olmaksızın tamamen veya kısmen kor ayrılması görülen dişler, tamir edilebilir (nonkatastrofik) kırık olarak isimlendirilir. Kırma testi sonrası örneklerde oluşan kırık tipleri incelendi. Kor seviyesinde ve koronal üçlü bölgesinde meydana gelen kırıklar tamir edilebilir olarak, daha apikal bölgede oluşan özellikle de vertikal şekilde meydana gelen kırıklar ise tamir edilemez kırıklar şeklinde değerlendirildi.

Çalışmamızda fiber post-kompozit kor grubunda 12, kompozit post-kor grubunda 4 ve lityum disilikat post-kor grubunda 4 dişte tamir edilebilir kırık izlenmiştir. Her bir grup için oluşan kırık tipleri Tablo 3'de gösterilmiştir. Fiber post-kompozit kor grubunda tamir edilebilir kırık tipinin oldukça fazla olduğu,ancak diğer gruplarda oluşan kırıkların büyük çoğunluğunun tamir edilemez olduğu belirlenmiştir.

Tablo 3: Gruplardaki Kırık Tiplerinin Sınıflandırılması

Gruplar	Tamir edilebilir kırık	Tamir edilemez kırık
Fiber post-kompozit kor	12 (%80)	3 (%20)
Kompozit post-kor	4 (%26,67)	11 (%73,3)
Lityum disilikat post-kor	4 (%26,67)	11 (%73,3)

TARTIŞMA ve SONUÇ

Bu çalışma ile ferrule desteği olmayan kök kanal tedavili dişlerin kırılma mukavemeti karşılaştırılmış ve üç farklı post-kor ile restore edilmiş dişlere uygulanan kuvvet sonucu oluşan kırılma tipleri incelenmiştir. Çalışma sonucunda lityum disilikat post-kor ve kompozit post-kor ile monoblok restore edilen dişlerin, fiber post-kompozit kor grubundan anlamlı olarak daha yüksek değerlerde kırılma direnci gösterdiği gözlendi. Ancak lityum disilikat post-kor ve kompozit post-kor grupları arasında kırılma direnci açısından anlamlı bir farklılık gözlenmedi. Böylece H0 hipotezi reddedilip ve H1 hipotezi kabul edilmiştir.

Post simantasyonu ve kor yapımı için farklı materyallerin kullanılması daha fazla adım gerektirir, bu da koltuk süresini ve materyaller arasındaki ara yüz etkileşim sayısını artırır. Monoblok tekniğinde sadece tek bir materyal kullanıldığından klinik prosedürler kolaylaştırılabilir, böylece zaman ve materyal tasarrufu sağlanır (9). Bitter ve ark., post simantasyonu ve kor yapımı için tek bir malzeme kullanılması ile, farklı malzemeler kullanılanılarak uygulanan post-kor sistemlerinde oluşabilecek olası uyumsuzlukların ortadan kaldırılabileceğini ve monoblok sistemin tam potansiyelini sağlayabileceğini vurgulamışlardır (10).

Tsukahara ve ark. sığır dişlerinde fiber post-kompozit kor, kompozit post-kor ve lityum disilikat post korların kırılma dayanımını inceledikleri çalışmada grupların kırılma dayanımı arasında anlamlı fark gözlenmemiştir (11). Bizim çalışmamızda farklı sonuç elde edilmesinin nedeni çalışmalarında kullandıkları dişleri kronlamaları ve sığır dişleriyle çalışmaları olabilir. Tsukahara ve ark. tüm gruplarda vertikal/tamir edilemeyen kırıkların daha fazla görüldüğünü belirtmiştir. Lityum disilikat post-kor ve kompozit post-kor grupları için çalışmamızla uyumlu sonuçlar elde edilmiştir. Ancak fiber post-kompozit kor grubunda bizim çalışmamızda tamir edilebilen kırık sayısı daha fazladır. Bu farklı sonucun sebebi daha uzun post kullanılması sebebiyle streslerin daha apikalde yoğunlaşıp tamir edilemez kırık meydana gelmesi olabilir.

Ekren ve arkadaşları (12) çalışmalarında döküm Ni-Cr post-kor, fiber post-kompozit kor ve lityum disilikat post-kor olacak şekide 3 post-kor gurubunun kırılma dayanımını incelemişlerdir. Lityum disilikat grubunun kırılma dayanımı anlamlı bir şekilde diğer gruplardan düşük değerler göstermiştir.Bu sonuçları bizim çalışmamız ile uyumlu değildir. Bizim çalışmamızdan farklı sonuçlar elde etmelerinin nedeni Ekren ve arkadaşlarının daha uzun (10 mm) post yuvası hazırlaması ve bu post yuvasının ölçüsünü akrilik rezin ile almaları sonucu kanal ile çok uyumlu olmayan bir post-kor elde edilmesi olabilir.

Pang ve ark. (13) çalışmalarında CAD/CAM ile hazırlanan cam fiberle güçlendirilmiş kompozit post-kor, cam fiber post-kompozit kor ve döküm altın post-kor gruplarının kırılma dayanımlarını karşılaştırmıştır. Bizim çalışmamızla uyumlu olacak şekilde monoblok post-kor olarak hazırlanan gruplarda yani cam fiberlerle güçlendirilmiş kompozit post-kor ve döküm altın post-kor gruplarında fiber post-kompozit kor grubuna göre daha yüksek kırılma dayanımları elde edilmiştir.

Bazı çalışmalar fiber postlu dişlerin kırılma paterninin kırılma sonrası daha iyi bir prognoza sahip olduğunu göstermiştir (14,15). Kırık tiplerini değerlendiren çalışmalara göre, fiber post kullanılan grupların çoğunda daha tamir edilebilir, sement-mine birleşiminin üzerinde seyreden kırıklar veya

köke kadar uzanmayan koronal kırıklar gözlenmiştir. Fiber postlar bu tip tamir edilebilir kırıklar ile diş yapısının kaybını önler ve dişin yeniden tedavi edilmesine izin verir (16). Bu bulgular çalışmamız ile uyumludur. Çalışmamızda sadece fiber post-kompozit post kor grubunda tamir edilebilir kırık sayısı ağırlıklıyken, kompozit post-kor ve lityum disilikat post kor gruplarında tamir edilemez kırık sayısı fazla gözlendi.

Araştırmacılar materyal ile komşu dokunun elastisite modülleri arasındaki farkın arttıkça stresin daha çok ara yüzeylerde yoğunlaştığını, simantasyon yüzeylerinde stresin artarak dentine ve simana daha az stres ilettiğini düşünmektedirler (17). Cam fiber postların dentine daha yakın bir elastik modüle sahip olduğu, bunun post/siman/dentin arayüzlerinde ve çiğneme aralıklı yüklemesi altında kalan diş yapısında düzgün bir stres dağılımı sağladığı ve böylece katastrofik kök kırığı riskini en aza indirdiği ileri sürülmektedir (18,19). Bu sebeple fiber post-kompozit kor grubunda daha az tamir edilemez kırık tipi gözlenmiş olabilir.

Fazla miktarda madde kaybına sahip endodontik tedavili dişlerin restorasyonunda kullanılan post-kor sistemlerinin kırılma dayanımının incelendiği bu çalışmada; bulgulara göre, fiber post-kompozit kor grubunda kırılma dayanımının düşük olduğu, ancak lityum disilikat ve kompozit post-kor gruplarında kırılma dayanımının birbirine yakın olduğu gözlemlenmiştir. Bu nedenle çok fazla madde kaybı olan dişlerin restorasyonunda fiber post yerine lityum disilikat post-kor ve kompozit post-kor tercih edilebilir. Ancak kırılma paternleri incelendiğinde; fiber post-kompozit kor grubunda tamir edilebilir kırıkların sayıca daha fazla olduğu görülmüştür. Lityum disilikat post-kor ve kompozit post-kor gruplarında ise tamir edilemez kırıkların daha fazla olduğu görülmüştür.

Bu in vitro çalışma dişlerin kırılma dayanımlarının değerlendirilmesinde in vivo durumu tam olarak yansıtmayabilir. Klinik performansı ve kabul edilebilirliği değerlendirebilmek için daha fazla uzun vadeli klinik araştırma gereklidir.

Etik Kurul Onayı: Bu çalışmada, "Yükseköğretim Kurumları Bilimsel Araştırma ve Yayın Etiği Yönergesi" kapsamında uyulması gerekli tüm kurallara uyulduğunu, bahsi geçen yönergenin "Bilimsel Araştırma ve Yayın Etiğine Aykırı Eylemler" başlığı altında belirtilen eylemlerden hiçbirinin gerçekleştirilmediğini taahhüt ederiz. Çalışma için Süleyman Demirel Üniversitesi Tıp Fakültesi Etik Kurulu'ndan 23.05.2023 tarih ve 116 sayılı karar ile etik kurul izni alınmıştır.

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The Role of Histopathology in the Diagnosis of Osteochondroma: Our Experience with Eighty-Eight Cases

Osteokondrom Tanısında Histopatolojinin Yeri: Seksen Sekiz Olgu ile Deneyimlerimiz

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ABSTRACT

Aim: Osteochondromas are the most common benign primary bone tumors with a medullary cavity, covered with hyaline cartilage, arising from the juxtaepiphyseal region of the bone. This study retrospectively evaluates cases diagnosed with osteochondroma presenting with varied localization and clinical findings, along with conventional cases, in light of current literature. Materials and methods: Hematoxylin-eosin and, where available, immunohistochemical stained preparations of samples from 88 patients diagnosed with osteochondroma between January 2010 and December 2023 at the pathology department of the Faculty of Medicine were evaluated. Age, gender, recurrence status, radiological findings, and clinical results were obtained from hospital records. The tumor localization and histopathological characteristics were retrospectively reviewed. Results: Among the 88 cases, 50 (56.8%) were male and 38 (43.2%) female, with ages ranging from 3 to 58 years. The mean age was 22.83, and the median age was 20. Most patients (n=55, 62.5%) presented with pain. Tumors were primarily located in the distal femur (n=33, 37.5%) and around the knee (47 cases, 53.4%). Grade II chondrosarcoma arising from osteochondroma was observed in only 1 case (1.1%). Conclusions: Osteochondroma is a primary benign bone tumor most commonly observed in males and frequently located in the distal femur. Pain is the most common clinical complaint, and surgical resection is the preferred treatment. Although osteochondromas are typically found in long bones, they may present with atypical localization and clinical findings. Malignant transformation, although rare, should be considered in osteochondromas.

Keywords: *Osteochondroma, Bone, Benign, Chondrosarcoma, Localization*

ÖZ

Amaç: Osteokondrom, kemiğin jukstaepifizer bölgesinden ortaya çıkan hyalin kıkırdak ile kaplı, kendi medüller boşluğu bulunan, iyi huylu, en sık primer kemik tümörüdür. Bu çalışmada konvansiyonel olgular ile birlikte farklı yerleşim ve klinik bulgular ile prezente olan osteokondrom tanılı olgularımızın retrospektif olarak değerlendirip, güncel literatür ışığında sunmayı amaçladık. Materyal ve metod: Tıp fakültesi Patoloji anabilim dalında Ocak 2010-Aralık 2023 yılları arasında osteokondrom tanılı 88 hastaya ait hematoksilen&eozin ve varsa immünhistokimyasal boyalı preparatlar retrospektif olarak değerlendirildi. Olguların yaş, cinsiyet, nüks durumları, klinik sonuçları hastane kayıtlarından elde edildi. Tümörün lokalizasyonu, radyolojik görüntüleme bulguları ve histopatolojik özellikleri retrospektif olarak değerlendirildi. Bulgular: Seksen sekiz olgunun, 50'si (%56,8) erkek, 38'i (%43,2) kadın olup olguların yaşlarının 3 ile 58 arasında değiştiği ve ortalama yaşın 22,83, ortanca yaşın ise 20 olduğu saptandı. Olguların en sık ağrı yakınması(n:55, %62,5) ile kliniğe başvurduğu tespit edildi. Tümörlerin en sık yerleşim yeri distal femur (n:33, %37,5) olup olguların büyük çoğunluğunda (47 olgu, %53,4) lezyon diz çevresinde lokalize idi. Yalnızca 1 olguda (%1,1) osteokondrom zemininde grade II kondrosarkomun geliştiği dikkati çekti. Sonuç: Osteokondrom erkek cinsiyette daha sık görülen, en sık distal femurda yerleşen kemiğin primer benign tümörüdür. Kliniğe en sık ağrı yakınmasıyla başvuran olgularda tedavi seçeneği cerrahidir. Osteokondromların çoğunluğu uzun kemiklerde görülmekle birlikte farklı, atipik lokalizasyon ve klinik bulgular ile karşımıza çıkabilirler. Nadir de olsa osteokondrom zemininde malign transformasyon gelişebileceği akılda tutulmalıdır.

Anahtar Kelimeler: *Osteokondrom, Kemik, Benign, Kondrosarkom, Lokalizasyon*

INTRODUCTION

Osteochondromas are the most common benign tumors of bone and are typically detected in the distal femur, proximal humerus, and tibia (1). Although almost all osteochondromas are solitary, an autosomal dominant form of osteochondromatosis, known as hereditary multiple exostoses (HME), can also be observed. Most of these cases are reported to be positive for mutations in the glycosyltransferase (EXT) genes (2,3). Understanding the pathogenesis is useful for increasing knowledge about the disease and can guide treatment. Genetic factors, abnormal embryological development, and growth and developmental disorders are involved in the pathogenesis of HME (4,5,6). Increased BMP signaling and the heightened activity of ranase, an enzyme that breaks down heparan sulfate chains and stimulates chondrogenesis, have also been reported to play a role in the pathogenesis; however, mutations in the EXT-1 and EXT-2 genes are most likely responsible (6, 7). EXT-1, located on chromosome 8q24.11-q24.13, has been detected in 28-65% of affected patients, while EXT-2, located on chromosome 11p11-12, has been detected in 21-61% of affected patients (5). EXT-1 and EXT-2 are genes that encode glycosyltransferases involved in the production of heparan sulfate, which binds to nuclear proteins in the cell membrane and facilitates the production of proteoglycans outside the cell. These mutations have not been detected in 5-34% of HME patients, suggesting that other EXT genes may also be involved in the pathogenesis (8).

Among the primary benign tumors of bone, osteochondromas account for approximately 35% in adults and 20-35% in pediatric patients (9).

Most osteochondromas, which some authors do not classify as true tumors, are asymptomatic (10). In terms of management, cases are typically monitored in the clinic, as they are benign tumors that usually do not cause symptoms. Complete surgical excision is indicated in cases of cosmetic concerns, bursal inflammation, secondary fracture formation, nerve paralysis, vascular compromise, pain, and, rarely, malignant transformation (11). The probability of recurrence after complete excision is less than 2% (2).

The rate of surgical intervention is higher in the osteochondromatosis form, which is six times less common than solitary osteochondroma, due to the increased risk of malignant transformation (12). In treatment protocols, asymptomatic, small, solitary masses do not typically require surgical intervention. One potential treatment option for such cases is retinoic acid receptor gamma (RARγ) agonists. Studies in mouse models have shown that these agonists can prevent heterotopic ossification and may reduce the number of osteochondromas (13,14). The incidence of osteochondromas has not been accurately determined based on histopathologically diagnosed cases, as most are detected incidentally through clinical evaluation and imaging methods, and surgical excision is not routinely performed (15).

Most cases are detected during the pediatric period. Thickening of the cartilage cap greater than 3 cm in pediatric patients and more than 2 cm in adults, along with reported pain and rapid growth of the lesion after puberty, raises suspicion for malignancy (2). The thickness of the cartilage cap can be misleading in younger patients, as this is the period when cellular proliferation peaks. Therefore, close follow-up in the clinic, along with evaluation of the mass and its behavior over time, is crucial (9). Symptoms resulting from vascular compression may include changes in skin color, loss of pulse, or alterations in blood flow. Patients may also develop arterial or venous thrombosis, aneurysms, or pseudoaneurysms. Given that the knee is the most commonly affected area, the popliteal artery, common peroneal nerve, and posterior tibial nerve are the structures most frequently involved (16).

Secondary chondrosarcomas may develop from existing osteochondromas. The onset of pain in a previously asymptomatic lesion should raise suspicion of malignant transformation (9). Transformation into chondrosarcoma occurs in approximately 5% of osteochondromas (17).

Amplification of MYC and AP-1 transcription factors plays a significant role in the pathogenesis of chondrosarcoma (18). Microscopic examination of chondrosarcoma may reveal necrosis and mitotic activity, and it can infiltrate cortical bone and the marrow space. Nuclear enlargement, hyperchromasia, size variation, and binucleation are characteristic features observed in chondrocytes. Chondrosarcomas are classified into four grades based on histopathological findings. Grade 1 chondrosarcomas closely resemble normal cartilage or enchondromas; thus, identifying an infiltrative pattern can assist in differentiation. Grade 2 exhibits more pronounced nuclear atypia, increased cellular size, and mitotic figures. In Grade 3, nuclear pleomorphism and atypia are readily apparent. Dedifferentiated chondrosarcoma has a poor prognosis and is characterized by spindle-shaped and pleomorphic cells devoid of a cartilage matrix. The IDH1 R132H antibody mutation is identified in approximately one-fifth of cases. Distinguishing Grade 1 chondrosarcoma from osteochondroma can be quite challenging, making it essential to evaluate these cases using imaging methods (19).

Osteochondromas are tumors that grow outward, manifesting as either pedunculated or sessile lesions, and are typically located in the metaphysis of bones. While direct radiography can be utilized alone for diagnosis, computed tomography (CT) and magnetic resonance imaging (MRI) are also valuable for measuring the thickness of the cartilage cap in cases where diagnosis is challenging or to predict potential complications (20).

A definitive diagnosis of osteochondroma is established through histopathological examination. Osteochondromas are characterized as hamartomatous lesions, exhibiting endochondral ossification with cartilage tissue present on the surface. Histopathologically, benign proliferation is observed with a medullary cavity, which is covered by hyaline cartilage, on the metaphyseal surface of the growth plate, known as the juxtaepiphyseal region. Expansion may be observed in the metaphyseal area where the tumor develops. Regardless of whether the tumor is pedunculated or sessile, the continuity of trabecular structures between the tumor and healthy bone is critical for diagnosis (21).

In this study, we aimed to retrospectively evaluate our cases diagnosed with osteochondroma, which presented with various localizations and clinical findings, alongside conventional cases, and to present our findings in the context of current literature.

MATERIAL and METHOD

Hematoxylin-eosin and immunohistochemically stained preparations, if available, from the materials belonging to 88 patients diagnosed with osteochondroma between January 2010 and December 2023 in Manisa Celal Bayar University Faculty of Medicine, Department of Medical Pathology were evaluated. This retrospective study was approved by the ethics committee of our institution, with approval date and number 27/12/2023/20.478.486/2172.

The hospital automation system provided information regarding the patients' ages, genders, presenting complaints, and the specific bone or bones in which the tumors were localized. Macroscopic images of the available materials in our archive concerning these cases were reviewed (sample macroscopic images are presented in Figures 1-6). The bone tissue samples, which were fixed in 10% buffered formalin and subsequently decalcified in 10% nitric acid solution, were sectioned to a thickness of 3-4 micrometers. Routine hematoxylin and eosin (H&E) stained slides, and additional immunohistochemical preparations deemed necessary were also evaluated (sample microscopic images are presented in Figure 7). In the radiology department, direct radiographs of the cases, along with available CT and MRI examinations on a case-by-case basis, were reviewed to confirm the localizations of the tumors (Figure 8).

Data analysis was conducted using SPSS version 21 (IBM, Chicago, IL, USA). The study included basic descriptive statistics such as frequency, percentage, arithmetic mean, standard deviation, and minimum and maximum values.

RESULTS

Among the 88 cases included in our study, 50 (56.8%) were male and 38 (43.2%) were female. The ages of the cases ranged from 3 to 58 years, with a mean age of 22.83 years and a median age of 20 years (Table 1).

Table 1. Distribution of Cases by Gender and Clinical Findings

Gender	**n**	**%**
Male	50	56,8
Woman	38	43,2
Total	88	100,0
Clinical Complaint	**n**	**%**
Swelling *	31	35,2
Pain	32	36,4
Pain+swelling	5	5,7
Pain+limitation of movement	18	20,5
Incidentally detected with a history of Trauma	2	2,3
Total	88	100

*Cosmetic reasons were noted in 1 of 31 cases in which swelling was detected.

Eighty-eight cases presented to the clinic, with pain being the most common symptom (n = 55, 62.5%). Among these cases, 32 (58.1%) reported pain only, 5 (9%) experienced pain accompanied by limitation of movement, and 18 (32.7%) had complaints of swelling along with pain. A history of trauma was noted in 1 of the 5 (20%) cases that had movement limitation along with pain. Additionally, in 2 cases, no symptoms were reported for the lesions; however, a mass was detected incidentally on radiographs taken due to trauma. Complaints of painless swelling were observed in 31 (35.2%) cases. In one instance, a 25-year-old male patient with an intra-articular mass reported cosmetic discomfort due to deformity as an additional complaint. Among the 5 cases with complaints of movement limitation, the lesion was located in the proximal femur in 2 cases, in the iliac region in 1 case, and intra-articularly in 2 cases (Table 1).

Of the 10 (11.3%) cases with multiple masses, 3 (27.2%) exhibited swelling, 2 (20%) had pain, and 5 (50%) presented with both pain and swelling. According to the tumor locations, the most common site was the distal femur (n = 33, 37.5%), followed by the proximal tibia (n = 14, 15.9%). It was noted that the lesions were around the knee in most of the cases (n = 47, 53.4%).

In the distribution of tumors according to localization, the humerus ranked third (n = 7, 8%), while the fingers ranked fourth (n = 6, 6.8%). Intra-articular tumors ranked fifth (n = 5, 5.7%), followed by the iliac and fibula bones (n = 4, 4.5%). The toes ranked sixth (n = 3, 3.4%), and the radius, distal tibia, and metacarpal bones each had 2 cases (n = 2, 2%). Lastly, the vertebrae, scapula, and metatarsal bones each had 1 case (n = 1, 1.1%) (Table 2, 3). Macroscopic images of tumors with different localizations and findings are presented in Figures 1-6.

Table 2. Distribution of Osteochondromas by Location and Form

Localization of osteochondroma	**n**	**%**
Distal Femur	33	37,5
Humerus	7	8,0
Proximal Femur	3	3,4
Proximal Tibia	14	15,9
Hand Phalanx	6	6,8
İliac Bone	4	4,5
İntra-Articular	5	5,7
Radius	2	2,3
Vertebra	1	1,1
Scapula	1	1,1
Fibula	4	4,5
Toe	3	3,4
Distal Tibia	2	2,3
Metacarpal	2	2,3
Metatarsal	1	1,1
Total	88	100,0
Form of osteochondromas	**n**	**%**
Solitary	78	88,6
Multiple	10	11,4
Total	88	100,0

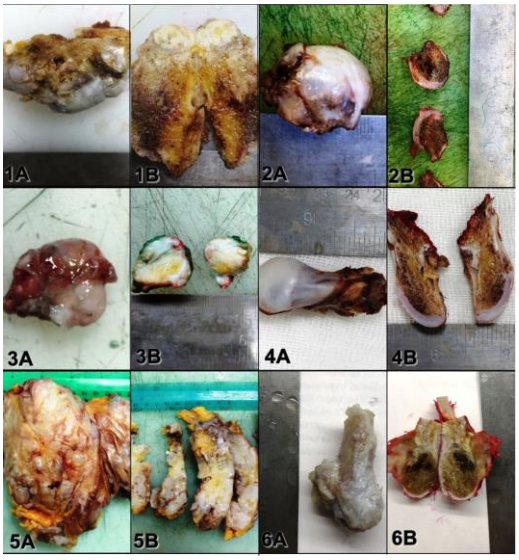

Figure 1-6: Macroscopic Samples Of Cases

1. Mass in the Proximal Tibia: (A) Excision material measuring 7 × 3.5 × 2.5 cm, with a bright pearlescent white outer surface and a lobular appearance, occasionally containing cartilage-like areas. **(B)** An area measuring 1.9 × 1.5 × 1.1 cm was observed in the distal part of the section surface, featuring a cream-colored cartilage surface; cartilage-like foci were also noted in other areas at the periphery of the lesion. **2. Mass in the Distal Femur: (A)** Hard, palpable bone excision material measuring 3.2 × 2.5 × 2.2 cm, with a shiny pearlescent white outer surface and occasional irregular brownish areas.**(B)** The cut surface was cream-brown, with a 0.3 cm thick cartilage-like area observed on the surface. **3. Mass on the 3rd Toe of the Left Foot: (A)** Bone excision material measuring 2.5 × 2 × 1.7 cm, exhibiting a bright and smooth appearance on the outside in most areas. **(B)** In the cross-sections, an area approximately 1 × 0.5 cm in the remaining half at the other end of the excision line appeared as smooth fibrous cartilage, while other areas were composed of cancellous bone. **4. Mass in the Distal Femur: (A)** Bone excision material measuring 4.7 × 2.2 × 1.8 cm, apparently excised from an area of 2.5 × 1.4 cm. Its outer surface was smooth, shiny, and white in color. **(B)** In cross-sections, the mushroom-shaped outer part was covered with 0.4 cm thick cartilage tissue, with spongiotic bone tissue visible in other areas. **5. Mass in the Distal Femur (Chondrosarcoma): (A)** Measuring 13 × 11 × 3.5 cm, this specimen exhibited a smoother appearance on one side, with a transparent-gray color and large and small nodular areas, while the opposite side contained mature fatty tissue in places and presented more irregular bone tissue. The material was composed almost entirely of tumors. **(B)** The cross-sectional surface consisted of tumoral areas with lobulated contours, appearing as transparent white-gray cartilage tissue. **(C)** Trabecular bone tissues invaded by the tumor were occasionally observed within the tumor areas, while some areas appeared to contain mature fatty tissue in the surrounding regions. **6. Left Hand 2nd Metacarpal Bone (NORA Lesion): (A, B)** Excision material of the bone measured 4 × 2.5 × 1.8 cm, cream-gray in color, and shiny. A nodular lesion was observed protruding 1.3 cm from the bone surface. **(C)** Upon incision of the lesion, the cut surface appeared dirty and cream-colored.

Table 3. Clinical Complaints of Cases and Distribution of Tumors by Location

Clinical Complaint	**LOCALIZATION**															n (t)
	1*	2*	3*	4*	5*	6*	7*	8*	9*	10*	11*	12*	13*	14*	15*	
Swelling	10	4	0	5	5	1	0	0	0	1	1	1	2	1	0	31
Pain	18	2	0	6	0	1	2	0	1	0	1	0	0	0	1	32
Pain+immobilization	0	0	2	0	0	1	2	0	0	0	0	0	0	0	0	5
Pain+Swelling	5	1	1	3	1	1	0	2	0	0	1	2	0	1	0	18
Incidental with Trauma	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	2
N (Total)	33	7	3	14	6	4	5	2	1	1	4	3	2	2	1	88

*localization: 1: distal femur, 2: humerus, 3: proximal femur, 4: proximal tibia, 5: fingers, 6: iliac, 7: intra-articular, 8: radius, 9: vertebra, 10: scapula, 11: fibula, 12:toes, 13: distal tibia 14: metacarpal 15: metatarsal

It was noted that grade II chondrosarcoma developed from osteochondroma in only 1 (1.1%) of all cases. In the case of a 45-year-old male diagnosed with chondrosarcoma, the mass was observed as a single localized mass in the distal femur. Malignant transformation was not observed in the other cases. Microscopic images of the tumors, displaying different findings, are presented in Figure 7.

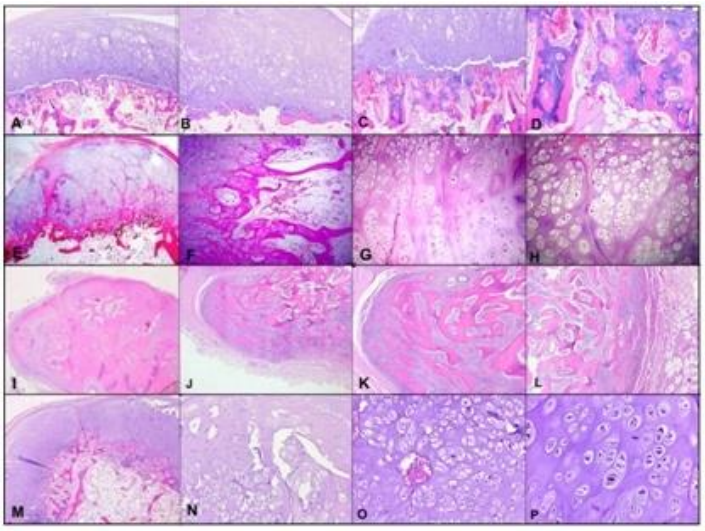

Figure 7: Microscopic Examination of the Samples

A-H: Photomicrographs of different osteochondroma cases. Osteochondroma consists of three layers; the perichondrium is visible on the outer surface, with a cartilage cap underneath that shows increased proliferation compared to normal bone. The tissue displays hyaline cartilage and irregular mature bone trabeculae passing through the cartilage. No significant atypia was observed in the proliferating chondrocytes. (H&E stained images; magnifications: x20, x40, x40, x100, x20, x100, x200, x200). **I-L:** Microscopic images from a case excised from the second metacarpal of a 15-year-old male patient, characterized by a proliferative lesion on the bone surface that is not connected to the bone cortex. The lesion, located in the stroma, is marked by spindle cell proliferation and contains limited areas of bone trabeculae and cartilage. Reactive nuclear enlargement was observed in chondrocytes within the cartilage areas. Osteoblasts and osteoclasts were noted at the periphery of the bone trabeculae. (H&E stained images; magnifications: x20, x20, x40, x40). **M-N:** Microscopic images of a 45-year-old male patient diagnosed with grade II chondrosarcoma arising from osteochondroma, localized as a single mass in the distal femur. A tumoral lesion displaying cellular hyaline cartilage morphology with lobulation was observed. The tumor showed areas of bone permeation. Foci of osteochondroma with a cartilage cap and spongy bone were noted. Most chondrocytes exhibited mild atypia, though some areas displayed more pronounced atypia with multiple chondrocytes found within the lacunae. (H&E stained images; magnifications: x20, x40, x100, x200).

In our study, a single mass was identified in 78 of the 88 cases (88.6%), while multiple masses were present in 10 cases (11.4%). Among the 78 cases with a single mass, 42 (53.8%) were male and 36 (46.2%) were female. The ages of these patients ranged from 3 to 55 years, with a median age of 20 and an average age of 23.28. In contrast, of the 10 cases with multiple masses, 8 (80%) were male and 2 (20%) were female, with ages ranging from 3 to 38 years; the median age was 20 and the average age was 19.3. Comparison of the ages of patients with single versus multiple masses revealed no statistically significant difference between the two groups ($p = 0.576$).

Among the 10 cases with multiple masses, the most common location was the distal femur (n = 3, 33.3%), followed by the humerus and proximal tibia (n = 2, 20% each), and the proximal femur, fibula, and toes (n = 1, 10% each). Radiographic images of osteochondromas, which can present as solitary or multiple masses in bone, are depicted in Figure 8.

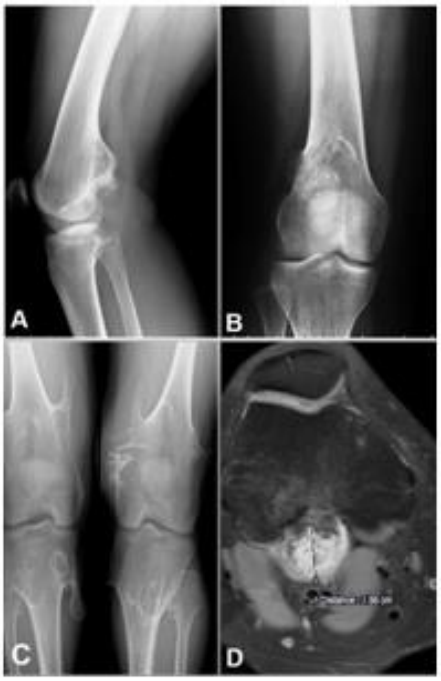

Figure 8: Direct Radiographs and MRI Examinations of The Case Were Conducted

Figure 8: A and B: Lateral and anteroposterior (AP) X-rays of the knee, showing a sessile osteochondroma located at the distal metaphysis of the femur, presenting as a bony exostosis continuous with the medullary bone. **C:** AP view X-ray of both knees demonstrating multiple pedunculated osteochondromas originating from the metaphyses of the bilateral femurs, tibias, and fibulas, typically projecting away from the epiphysis. **D:** Axial proton density (PD) fat-saturated MRI of the distal femur revealing a benign osteochondroma located at the distal metaphysis, with a cartilage cap measuring less than 2 cm in thickness.

DISCUSSION and CONCLUSION

It has been reported that osteochondromas are three times more common in men than in women (22,23). In another study, the incidence of osteochondroma in women was found to be half that of men (24). A study that focused solely on solitary osteochondromas did not identify a significant difference between male and female patients (25). In our study, we observed a higher prevalence of osteochondromas among male cases (n: 50, 56.8%) compared to female cases (n: 38, 43.2%). Additionally, we noted a greater proportion of osteochondromas in patients with multiple lesions than in those with solitary tumors.

Research indicates that osteochondromas are predominantly observed during the first and second decades of life (24,26,27). In our cohort, which included cases ranging from 3 to 58 years of age, we found that the majority fell within the first and second decades (mean age: 22.83 years; median age: 20 years), consistent with existing literature.

In a study comprising fifty-six cases, it was reported that a small subset exhibited symptoms of pain and localized swelling, while the remainder were diagnosed incidentally through radiographs taken for other reasons (28). In our study, we found that patients most frequently presented to the clinic with complaints of pain (n: 32, 58.1%), followed by swelling (n: 18, 32.7%). Among the five cases (9%) that experienced limited movement in conjunction with pain, one case had a notable history of trauma. Additionally, two cases were incidentally diagnosed with osteochondroma following trauma. Painless swelling was reported in 31 cases (35.2%), with cosmetic concerns identified in one instance.

Most of the cases associated with limited mobility involved masses located in bones related to the hip joint, specifically the iliac bone, proximal femur, and intra-articular regions. Although rare, osteochondromas can lead to compression of adjacent neurovascular structures, resulting in entrapment neuropathy of deep nerves. Neurological symptoms such as radiculopathy and myelopathy may arise in tumors that grow toward the spinal canal (29, 30).

Osteochondromas are most commonly found in the distal femur (30%), followed by the proximal tibia (15-20%), humerus (10-20%), hands and feet (10%), pelvis (5%), scapula (4%), and vertebrae (2%) (31). While the literature indicates that these tumors are predominantly detected in the knee region, one study identified the distal fibula as the third most common site, displacing the humerus from that position (24). In our study, the tumor was most frequently localized in the distal femur (n: 33, 37.5%), with the proximal tibia being the second most common site (n: 14, 15.9%). Notably, the mass was located around the knee in the majority of cases (47 cases, 53.4%).

Osteochondromas have been reported in the rib cage and pelvis in approximately 5% of cases, with an even smaller proportion found in the vertebrae (32,33). In our study, no tumors were detected in the rib cage; however, a higher incidence of tumors was noted in the iliac bone (4.5%, n: 4) compared to existing literature. Additionally, we documented one case each in the vertebra and scapula, which represent rare localizations.

In a study evaluating seven hundred and forty-eight solitary osteochondromas, tumors were identified in the bones of the foot in 10 cases, with only 2 of these located specifically in the forefoot bones (20). In our study, osteochondromas were observed in the toes in 3 cases (3.4%) and in the metatarsal bones in 1 case (1.1%). Additionally, tumors were detected in the fingers of the hands in 6 cases (6.8%) and in the metacarpal bones in 2 cases (2.3%).

According to Lichtenstein et al., the prevailing hypothesis is that osteochondromas arise spontaneously as a result of a reaction in the periosteum, triggered by rapid proliferation (34,35). Conversely, other authors propose that the development of osteochondromas may be attributed to endogenous factors (genetic predisposition) or exogenous influences (such as trauma or radiation) (11,22).

Osteochondroma can have several mimics, including subungual exostosis, bizarre parosteal osteochondromatous proliferation (BPOP), also known as Nora lesion, florid reactive periostitis, dysplasia epiphyseal hemimelica (Trevor disease), and turret exostosis (16).

The NORA lesion, also known as bizarre parosteal osteochondromatous proliferation, is a benign bone lesion characterized by a high recurrence rate and various morphological findings. It is primarily observed in the small bones of the hands, infrequently in the bones of the feet, and very rarely in larger bones (36). During our study, a case of NORA lesion that posed a challenge for differential diagnosis was identified in our archives. This case involved a 15-year-old male patient, in whom the lesion was localized to the second metacarpal region of the hand and was noted to have local recurrences during follow-up in the clinic. Histopathological examination revealed bone trabeculae and cartilage areas within the stroma, characterized by spindle cell proliferation on the bone surface, which showed no connection to the underlying bone cortex. Occasional nuclear enlargement of chondrocytes was also observed.

In addition to NORA lesion, the differential diagnosis encompasses parosteal osteosarcoma, subperiosteal hematoma, exostoses (including Dupuytren and turret exostoses), and enchondromas, all of which lack continuity with the intact bone medulla (37). The assessment of continuity with the bone medulla is crucial for making an accurate histopathological diagnosis.

Osteochondromas can lead to neurological complications in the extremities due to pressure exerted on nearby nerves, as well as vascular complications arising from pressure on vascular structures. Neurological issues may manifest as neuropathic pain or result in a loss of strength. Vascular complications can range from thrombosis to alterations in blood flow, potentially leading to ischemia due to insufficient nutritional supply to the tissues (2). The overall prognosis for osteochondromas is very favorable, with a recurrence rate estimated at approximately 2% (38). In our cases, no additional complications were reported following surgery, and no recurrences were observed.

Although a definitive diagnosis is established histopathologically, pathognomonic features of osteochondromas can often be identified through plain radiographic imaging. These lesions may appear as stalked or flat protrusions emerging from the surface of the bone and are typically located in areas where tendons attach to long bones, which can result in widening of the metaphysis. Expected radiographic findings include calcifications or linear extensions within the cartilage structure (39). In our study, the final diagnosis was achieved by analyzing the radiological images of the cases and correlating our histopathological findings with clinical and imaging data.

The periosteal reaction and the irregularity of tumor edges observed in osteosarcoma, which is included in the differential diagnosis on imaging, are significant diagnostic factors (40). Secondary osteosarcoma, which may arise from osteochondroma, is exceedingly rare (41). In our study, no instances of osteosarcoma secondary to osteochondroma were identified.

Chondrosarcoma is characterized by a low signal on diffusion-weighted MRI (26). In cases of malignant transformation, the thickness of the cartilage cap and the enhancement of septa using gadolinium are critical for diagnosis (42). Distinguishing between osteoblastic proliferation observed in chondrosarcoma and endochondral ossification seen in osteochondroma can be challenging using bone scintigraphy. Positron emission tomography (PET) may aid in grading and diagnosing chondrosarcoma; however, it is important to note that abnormal glucose retention can occur in osteochondromas, which are common in the pediatric population and continue to grow during this period (43). A study examining solitary osteochondromas over a span of 32 years reported recurrence in six cases, with secondary chondrosarcoma detected in two (43). It is estimated that 80% of secondary chondrosarcomas develop from osteochondroma. These secondary chondrosarcomas typically present at an earlier age (approximately 35 years) compared to primary chondrosarcomas, with a reported risk of malignant transformation of about 2% in cases with chondromatosis. Notably, nearly half of these cases involve the pelvic bone (9). In our study, we documented the development of grade II chondrosarcoma from osteochondroma in a 45-year-old male patient (1.1%). No malignant transformations were noted in the other cases, and the chondrosarcoma was identified as a single mass located in the distal femur.

The incidence of secondary chondrosarcomas arising from osteochondromas is estimated at 1-2%. While this rate is elevated in cases of osteochondromatosis, the actual percentage may be lower, as many solitary osteochondromas remain asymptomatic and are often discovered incidentally (26). In another study, it was determined that 81% of 151 chondrosarcoma cases developed from osteochondroma (44). In our study, no malignant transformations were observed in any of the multiple osteochondroma cases.

Secondary chondrosarcomas are typically diagnosed in individuals in their fifth and sixth decades, whereas primary chondrosarcomas are generally identified at a younger age (45). The case of grade II chondrosarcoma arising from osteochondroma that we documented in our study was in a 45-year-old patient, aligning with the typical age range for secondary chondrosarcomas.

Microscopic examination reveals several signs indicative of malignant transformation, including increased mitosis, atypical mitosis, necrosis, hypercellularity, cystic and myxoid changes, distortion of architecture, and nuclear pleomorphism (45). In the histopathological analysis of the grade II chondrosarcoma arising from osteochondroma, identified in our study, the tumor exhibited lobulated cellular morphology of hyaline cartilage with evidence of bone permeation. Mild atypia was noted in most areas, while atypical features became more pronounced in certain regions, where multiple chondrocytes were observed within the lacunae.

For symptomatic osteochondromas, particularly those with cosmetic concerns, irregular borders, radiolucent foci, or suspicious imaging characteristics such as bone destruction, the most appropriate management involves radical excision that includes the cartilage cap. This should be accompanied by close clinical follow-up to monitor for potential recurrence, and postoperative radiotherapy should be considered if necessary. Additionally, in cases where the tumor's localization may lead to instability after procedures such as laminectomy or fasciectomy, surgical stabilization is recommended. Although malignant transformation is infrequent, careful assessment is warranted in cases where the cartilage cap measures over 3 cm, particularly in conditions like Multiple Hereditary Exostoses (MHE), where the risk of malignant transformation is elevated. In such scenarios, postoperative radiotherapy should be considered alongside rigorous clinical and radiological follow-up (46,16).

Osteochondroma is primarily a benign bone tumor that is more prevalent in males and is most commonly located in the distal femur. Patients typically present with complaints of pain, although recurrence is rarely observed. While the majority of osteochondromas occur in long bones, they may manifest with atypical localizations and clinical presentations. Osteochondromas can be solitary or multiple, with most cases being solitary in nature. It is important to remain vigilant for the possibility of malignant transformation, albeit rare, occurring in association with osteochondroma.

Declaration of Ethical Code: This retrospective study was approved by the ethics committee of our institution with date and number 27/12/2023/20.478.486/2172

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Evaluating the Role of Disease Duration in Fatigue and Quality of Life Among Rheumatoid Arthritis Patients

Romatoid Artrit Hastalarında Hastalık Süresinin Yorgunluk ve Yaşam Kalitesi Üzerindeki Rolünün Değerlendirilmesi

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ABSTRACT

Objective: The duration of a disease plays a critical role in understanding its progression and impact on an individual's quality of life and symptom severity. The aim was to investigate the effect of disease duration on fatigue and quality of life in patients with rheumatoid arthritis (RA). Material and Methods: The cross-sectional study included ninety-two (female:71, male:21) patients with RA. Clinical and demographic characteristics of patients were recorded. Disease activity (Disease Activity Score in 28 joints with CRP (DAS28-CRP)), fatigue (Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire (BRAF-MDQ)), and quality of life (Short Form-36 questionnaire (SF-36)) were evaluated in the study. RA patients were categorized into two groups based on the disease duration: duration of the disease <10 years and duration of the disease >10 years. Results: Significant differences were found in the pain (p=0.022), general health (p=0.028), and health change (p=0.020) subdomains of SF-36. However, BRAF-MDQ scores and its subdomains showed no significant differences across groups. Conclusion: While the duration of RA significantly affects certain aspects of quality of life such as pain and general health, it does not appear to influence fatigue levels. This highlights the persistent and debilitating nature of fatigue in RA patients regardless of disease duration, emphasizing the need for targeted interventions to address this symptom.

Keywords: *Rheumatoid arthritis, Fatigue, Quality of life, Disease duration*

ÖZ

Amaç: Hastalık süresi, hastalığın ilerleyişini ve hastaların yaşam kalitesi ile semptom şiddeti üzerindeki etkilerini anlamada kritik bir rol oynamaktadır. Bu çalışmanın amacı, romatoid artrit (RA) hastalarında hastalık süresinin yorgunluk ve yaşam kalitesi üzerindeki etkisinin araştırılmasıdır. Materyal ve Metot: Enine kesitsel çalışmada, 92 (kadın:71, erkek:21) RA hastası analiz edildi. Hastaların klinik ve demografik özellikleri kaydedildi. Hastalık aktivitesi (Hastalık Aktivite Skoru (DAS28)), yorgunluk (Bristol Romatoid Artrit Yorgunluk-Multidimensional Anketi (BRAF-MDQ-T)) ve yaşam kalitesi (Kısa Form-36 anketi (SF-36)) değerlendirildi. RA hastaları hastalık süresine göre iki gruba ayrıldı: hastalık süresi <10 yıl ve hastalık süresi >10 yıl. Bulgular: SF-36 alt alanları olan ağrı (p=0,022), genel sağlık (p=0,028) ve sağlık değişimi (p=0,020) açısından anlamlı farklar bulundu. Ancak, BRAF-MDQ-T skorları ve alt alanları gruplar arasında anlamlı fark göstermedi. Sonuç: RA hastalarında hastalık süresi, ağrı ve genel sağlık gibi bazı yaşam kalitesi alanlarını önemli ölçüde etkilerken, yorgunluk seviyelerini etkilemediği bulundu. Bu durum, RA hastalarında yorgunluğun sürekli ve zayıflatıcı doğasını vurgulamakta ve bu semptomu ele alacak hedefe yönelik müdahalelerin gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: *Romatoid artrit, Yorgunluk, Yaşam kalitesi, Hastalık süresi*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disorder that predominantly affects small joints, leading to pain, joint destruction, and disability. This autoimmune disease can also involve extra-articular manifestations such as cardiovascular, pulmonary, and gastrointestinal complications, rheumatoid nodules, and vasculitis (1).

Among the myriad of symptoms, fatigue is one of the most debilitating, affecting more than 70% of RA patients. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recognized fatigue as a critically important outcome for patients with RA and have recommended that fatigue be systematically reported in all clinical trials involving RA patients (2). Based on pieces of evidence, this fatigue is often described as pervasive, overwhelming, and debilitating, significantly impacting daily activities and overall quality of life (QoL) (3). The multifaceted nature of fatigue in RA patients is influenced by several factors. Persistent joint pain and stiffness exacerbate the sensation of fatigue, while the psychological burden of managing a chronic disease further compounds it (4, 5). Additionally, the inflammation and immune dysregulation inherent in RA demand substantial energy from the body, intensifying fatigue. Furthermore, medications used to manage RA, such as disease-modifying antirheumatic drugs, may also contribute to fatigue (6, 7).

RA's impact extends beyond the physical symptoms, affecting patients' emotional and social well-being (8). The condition can lead to feelings of isolation, depression, and anxiety, which further deteriorate QoL (8, 9). The profound effects of RA on individuals extend to their families, friends, and caregivers, influencing relationships, work productivity, and daily activities. Addressing these challenges requires a comprehensive approach that encompasses both the physical and emotional aspects of the disease (10). A study has shown that early diagnosis and intervention can significantly improve the quality of life for patients with RA. Medical treatments combined with lifestyle modifications, such as exercise, stress management, and a healthy diet, are crucial in managing symptoms and improving well-being (11).

The primary objective of this study is to assess the impact of disease duration on fatigue and quality of life in RA patients. The null hypothesis of the study was that the duration of the disease does not affect fatigue and quality of life in patients with rheumatoid arthritis. The alternative hypothesis of the study was that the duration of the disease does affect fatigue and quality of life in patients with rheumatoid arthritis. By examining the relationship between how long patients have been living with RA and the severity of their fatigue and quality of life, the study aims to provide a deeper understanding of the disease's progression and its broader implications for patient health and well-being. Understanding the relationship between disease duration and these critical aspects can provide insights into better management strategies for RA patients. Additionally, by analyzing how the length of time a patient has RA influences their experience of fatigue and overall QoL, this study seeks to identify potential areas for intervention that may improve patient outcomes.

MATERIAL and METHOD

Study Design

The cross-sectional study received approval from the Bingöl University Ethics Committee (dated:16/04/2024, no:24/9), in accordance with the principles outlined in the Helsinki Declaration. The study was carried out at the Clinic of Rheumatology, Ankara Etlik City Hospital. Before beginning this study, all patients signed an informed consent form.

Patients

The inclusion criteria comprised the following: 1) Patients aged between 18 and 70 years who met the 2010 ACR/EULAR criteria for RA (12); 2) using a regular medication regimen for RA; 3) stable general health condition for the previous 6 months (having no significant illnesses or laboratory abnormalities that require hospitalization or major treatment modifications).

Patients who had a history of malignancies, cognitive deficits, receiving antipsychotic treatment, pregnancy, alcohol dependence, fibromyalgia syndrome, other rheumatic diseases besides RA, neurological diseases such as stroke, multiple sclerosis, and illiterate patients were excluded. Patients with RA who met the inclusion criteria were selected using a probability simple random sampling method.

The post-hoc power analysis was performed with G*Power 3.1.2.1 software (version 3.1.9.2, Franz Faul, University of Kiel, Kiel, Germany). Ninety-two included patients were found to provide a power of 0.824, based on a Type 1 error rate (alpha=0.05), effect size of 0.55 (considered a medium effect with d≥0.5), and a one-tailed hypothesis. Therefore, the present sample size was deemed to be sufficiently powered.

RA patients were categorized into two groups based on the disease duration: duration of the disease <10 years and duration of the disease >10 years.

Data Collection

Sociodemographic characteristics, including age, body mass index, smoking history, smoking exposure, marital status, occupation, were obtained. The duration of disease was also recorded. Disease activity of the participants was assessed with Disease Activity Score-28- C-reactive protein (DAS-28-CRP) (13). All participants were questioned to complete the Short Form- 36 (SF-36) questionnaire for quality of life (14) and the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ) for fatigue (15).

The Disease Activity

A rheumatologist evaluated the disease activity of patients with RA by utilizing the DAS-28-CRP (13). The DAS28-CRP score is calculated by considering the number of tender joints, number of swollen joints, CRP levels, and the global evaluation score. The DAS28 CRP score was categorised as follows: 0-2.6 for remission, 2.6-3.2 (including 3.2) for low disease activity, 3.2-5.1 (including 5.1) for moderate disease activity and above 5.1 for high disease activity (13).

The Quality of Life

The SF-36 is a widely used generic health-related quality of life questionnaire designed to evaluate various aspects of well-being. It encompasses eight subscales, each focusing on different domains (16, 17). Higher scores reflect to a higher quality of life on each subscale, which is scored from 0 to 100 (14). A validity and reliability study was conducted on the scale in Turkish (17).

The Fatigue

The BRAF-MDQ is a tool utilized to assess the impact of fatigue among patients with RA across various dimensions (15, 18). Comprising a total of 20 items, the BRAF-MDQ encompasses four subdomains: physical fatigue, fatigue in activities of daily living, cognitive fatigue, and emotional fatigue. All items except the first 3 items are asked to be answered according to a 4-point Likert system (0: not at all, 1: a little, 2: quite a bit and 3: very much). The first 3 items are scored as follows: item-1 is between 0-10, item-2 is between 0-7, and item-3 is between 0-2. The questionnaire evaluates the last seven days. Higher scores indicating elevated levels of fatigue (15, 18). Turkish translation and psychometric properties of the BRAF-MDQ was performed by Sari et al. (15).

Statistical Analysis

Statistical Package for the Social Science (SPSS, version 22.0) software was utilized to analyze the data. Visual and analytical tests (Kolmogorov-Smirnov test) were used to test the normality of data. The data are showed as number (percentage) for categorical data, mean (standard deviation) for continuous variables with a normal distribution, and median (interquartile range) for variables without a normal distribution. The sociodemographic and clinical characteristics of the groups (duration of the disease <10 years versus duration of the disease >10 years) were compared with the

independent sample t test or Mann-Whitney U test for parametric data and Fisher's exact test or Pearson chi-square test for categoric data. The Independent Samples t-test was performed to compare the BRAF-MDQ and its subdomains results between the groups. For all statistical significance, a p-value of less than 0.05 was used.

RESULTS

A total of ninety-two individuals with RA (71 female, 21 male; mean age: 55 (12.8); mean BMI: 28.1 (5.7) kg/m^2) were included in the current study. The mean DAS28-CRP score of patients was 3.1 (0.7) and the median duration of the disease was 7 (3-13.5) years. Most patients were housewives (n=54, 58.7%) and non-smokers (n=67, 72.8%). The groups were similar in terms of clinical and demographic characteristics (p>0.05). The demographic and clinical characteristics of the patients are indicated in Table 1.

In comparing the SF-36 results based on the duration of the disease, a significant difference was found between the groups regarding pain (p=0.022), general health (p=0.028), and health change (p=0.020). The comparison of the SF-36 results based on the duration of the disease is indicated in Table 2.

The BRAF-MDQ (p=0.475) and its subdomains, including physical (p=0.738), living (p=0.091), cognitive (p=0.400), and emotional fatigue (p=0.270), were similar between the groups. The comparison of the BRAF-MDQ and its subdomains based on disease duration is illustrated in Figure 1.

Table 1: Demographic and Clinical Characteristic of Patients

	RA (All patients) (n=92)	Duration of the disease <10 years (n=54)	Duration of the disease >10 years (n=38)	p value
Age (year), mean (SD)	55 (12.8)	52.9 (13.1)	57.9 (12)	0.064*
Gender, n (%)				
Female	71 (77.2)	39 (72.2)	32 (84.2)	0.214[a]
Male	21 (22.8)	15 (27.8)	6 (15.8)	
BMI (kg/m^2), mean (SD)	28.1 (5.7)	28.1 (5.2)	28.1 (6.4)	0.999*
DAS28, mean (SD)	3.1 (0.7)	3.1 (0.6)	3.2 (0.8)	0.432*
Disease duration (year), median (IQR)	7 (3-13.5)	4 (2-6)	15 (10-20)	<0.001[b]
History of smoking, n (%)				0.396[c]
None	67 (72.8)	40 (74.1)	27 (71.1)	
Active	8 (8.7)	6 (11.1)	2 (5.3)	
Ex-smoker	17 (18.5)	8 (14.8)	9 (23.7)	
Smoking exposure, packet*year, median (IQR)	16 (12-40)	15 (12-20)	35 (10-40)	0.458[b]
Existing of comorbidity, n (%)	50 (54.3)	28 (51.9)	22 (57.9)	0.672[a]
Education level, n (%)				
Primary School	42 (45.7)	25 (46.3)	17 (44.7)	
Middle School	7 (7.6)	3 (5.6)	4 (10.5)	
High School	22 (23.9)	15 (27.8)	7 (18.4)	0.659[c]
University	18 (19.6)	10 (18.5)	8 (21.1)	
Master's degree	3 (3.3)	1 (1.9)	2 (5.3)	
Marital status, n (%)				
Married	68 (73.9)	43 (79.6)	25 (65.8)	0.161[c]
Single	6 (6.5)	4 (7.4)	2 (5.3)	
Divorced	18 (19.6)	7 (13)	11 (28.9)	
Occupation, n (%)				
Housewife	54 (58.7)	31 (57.4)	23 (60.5)	
Student	2 (2.2)	2 (3.7)	0 (0)	0.065[c]
Active worker	13 (14.1)	11 (20.4)	2 (5.3)	
Retired	23 (25)	10 (18.5)	13 (34.2)	

SD: Standard Deviation; IQR: Interquartile range; DAS28: The Disease Activity Score-28
*Independent sample t test
[a] Fisher's exact test
[b] Mann-Whitney U test
[c] Pearson chi-square test

Table 2: The Comparison of The SF-36 Results Based on The Duration of The Disease

	Duration of the disease <10 years (n=54) Median (IQR)	Duration of the disease >10 years (n=38) Median (IQR)	p value*
Physical function	50 (15-75)	35 (10-55)	0.050
Role limitations due to physical health	37.5 (0-100)	0 (0-75)	0.106
Role limitations due to emotional problems	33.3 (0-100)	0 (0-100)	0.737
Energy/fatigue	50 (30-60)	32.5 (15-55)	0.056
Emotional well-being	60 (48-76)	56 (40-80)	0.469
Social function	62.5 (37.5-87.5)	50 (37.5-87.5)	0.766
Pain	67.5 (32.5-90)	43.7 (20-77.5)	**0.022**
General health	55 (35-70)	45 (25-55)	**0.028**
Health change	75 (25-75)	50 (25-75)	**0.020**

IQR: Interquartile range.
*Mann-Whitney U test

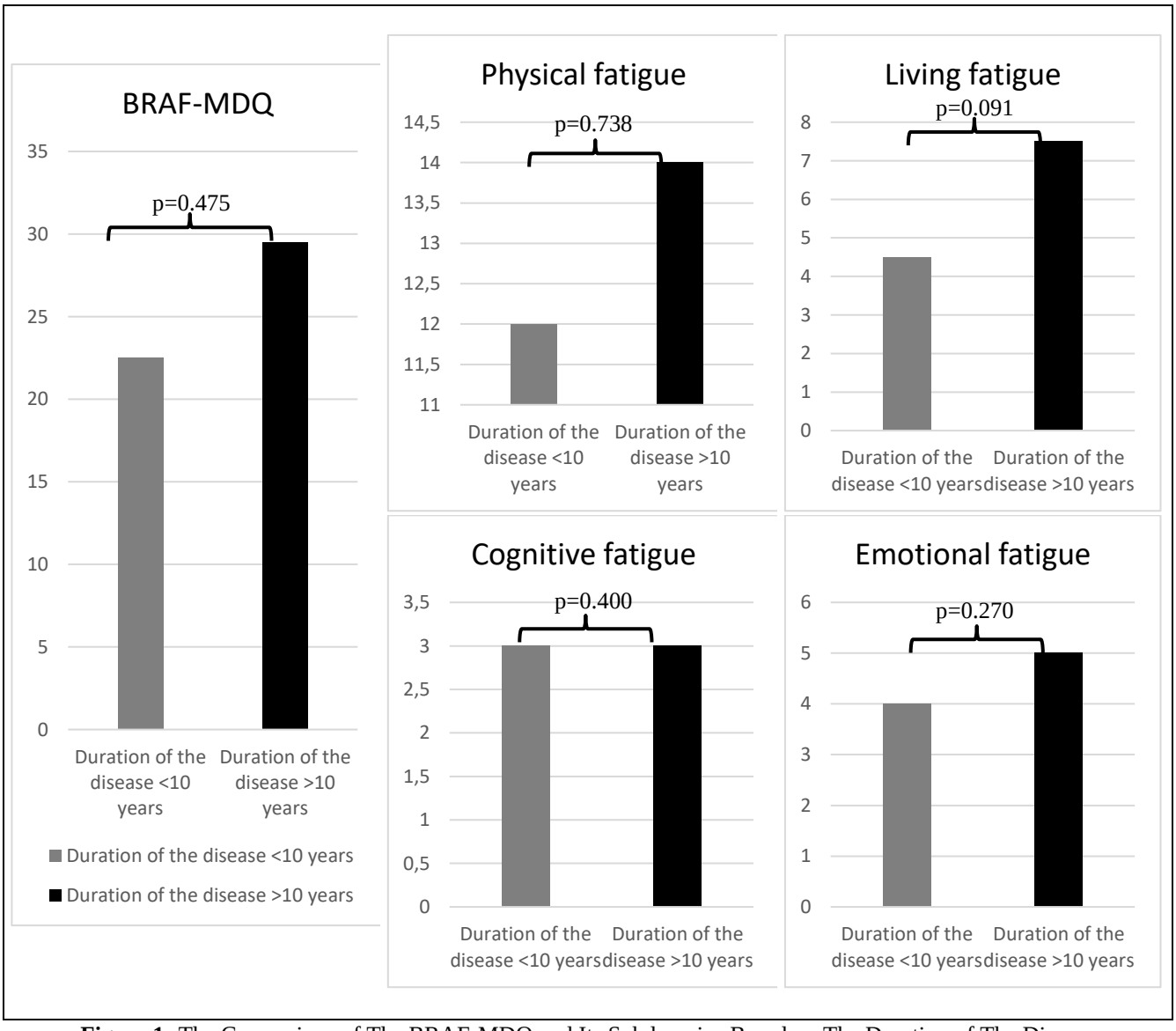

Figure 1: The Comparison of The BRAF-MDQ and Its Subdomains Based on The Duration of The Disease

DISCUSSION and CONCLUSION

The results of the current study offer significant insights into the influence of disease duration on fatigue and QoL in patients with RA. Our findings highlight several significant differences in the experiences of patients with shorter versus longer disease duration, particularly in terms of pain, general health, and perceived health changes.

Numerous studies in the literature have demonstrated that QoL is significantly lower in RA patients compared to the healthy population (8, 9, 19). Consistent with previous studies, our findings revealed that patients in both groups exhibited lower scores in the SF-36 subgroups. A meta-analysis indicates that RA significantly impairs QoL, with pooled scores from the SF-36 showing that physical domains are more adversely affected than mental health domains. This suggests that RA has a more substantial impact on physical QoL compared to mental well-being (19). Furthermore, several studies have emphasized the association between disease duration and SF-36 subgroups (20, 21). Kiebles et al. demonstrated a significant positive relationship between disease duration and overall emotional well-being, as well as role limitations due to emotional problems, indicating that patients with a longer duration of symptoms may exhibit a greater level of acceptance of their condition compared to those with recent onset disease (20). In contrast, Barlow et al. found no statistically significant differences in QoL between patients with short disease duration (≤1 year) and those with longer disease duration (≥10 years) (22). However, the current study indicated that QoL, specifically regarding pain, general health, and health change, decreased in the group with a long disease duration (>10 years). There are varying results regarding the relationship between disease duration and QoL in RA patients in the literature. While this relationship has not yet been conclusively demonstrated in an RA population, studies on other inflammatory conditions have found a significant correlation between disease duration and increased disease acceptance. Therefore, when evaluating disease duration and other symptoms in RA patients, assessing their level of disease acceptance is important.

It was anticipated that longer disease duration, resulting in joint erosions and prolonged suffering, would correlate with higher fatigue levels. Two cross-sectional studies found a significant relationship between longer disease duration and fatigue (23, 24). Belza et al. proposed that fatigue is primarily influenced by disease- and sex-related factors, such as disease duration, functional status, and sleep quality (23). In contrast, one cross-sectional study (25) and two longitudinal studies (26, 27) did not find an association between disease duration and fatigue. Similarly, a systematic review indicated that RA patients experience significant fatigue in the early and later stages of the disease (28). Similarly, disease duration was not found to influence fatigue levels in our study. Notably, our findings indicate fatigue levels are significantly high from the onset of the disease and do not vary with disease duration. Consistent with these studies, our study did not identify any difference in fatigue levels between patient groups with a disease duration of less than 10 years and those with more than 10 years. RA patients experience significant fatigue both in the early and later stages of the disease. The possible mechanisms underlying these parameters remain unclear, indicating the need for further studies to elucidate the relationship between disease duration and fatigue.

The present study has some limitations. Firstly, patients were not compared based on disease activity. Secondly, we did not consider the patients' economic and socio-cultural levels in the study. Thirdly, patients were not asked about exercise habits or physical activity levels that could directly impact fatigue. Additionally, while disease acceptance may influence patients' perceptions of fatigue and quality of life, our study did not examine this aspect, representing another limitation. Fatigue affects patients from the onset of the disease; therefore, future research should investigate the underlying mechanisms of persistent fatigue in RA and identify targeted interventions to decrease this debilitating symptom. Understanding the interplay between disease duration, inflammation, and fatigue can lead to more effective treatments and support for RA patients. Additionally, longitudinal

studies that track changes in fatigue and QoL over time in response to different treatment regimens would provide deeper insights into managing RA more effectively.

This study highlights that while disease duration in RA significantly affects pain, general health, and health change, its impact on fatigue is not clear-cut. Comprehensive care strategies that address immediate and long-term health challenges are essential for improving the quality of life for RA patients.

Acknowledgment: Thank you to all our patients who completed the study.

Declaration of Ethical Code: In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

The study received approval from the Bingöl University Ethics Committee (dated:16/04/2024, no:24/9), in accordance with the principles outlined in the Helsinki Declaration. Before beginning this study, all patients signed an informed consent form.

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The Acute Effects of Aerobic Exercise on Cognitive Functions in Young Adults

Genç Yetişkinlerde Aerobik Egzersizin Kognitif Fonksiyonlar Üzerine Akut Etkilerinin İncelenmesi

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ABSTRACT

Objective: The acute effects of aerobic exercise on cognitive function in young adults are well-established, yet the acute effects of exercise on cognitive function remain incompletely understood. We aimed to investigate the acute effects of 1-session aerobic exercise on cognitive functions in healthy young adults. The study included 52 healthy young adults (24 males, 28 females) studying at the Faculty of Physiotherapy and Rehabilitation between 2020 and 2022. Material and Method: The exercise routine consisted of a 5-minute warm-up, followed by a 20-minute period of increased intensity, and concluded with a 5-minute cool-down. We employed the Stroop Test to evaluate the participants' attention levels. In addition, the number sequence (SD) subtest of the Wechsler Memory Scale-Generalized Form (WMS-G) was used to assess the participants' memory level pre- and post-exercise. Results: The mean age of the participants was 23.34±1.13 years. The participant showed significant improvement in stroop test times but not for number of correct and errors (Stroop 1, stroop 2, stroop 3, stroop 4, and stroop 5= $p< 0.0001$, $p< 0.008$, $p< 0.0001$, $p< 0.0001$, and $p< 0.001$, respectively). The participant showed no significant improvement in WMS-G values (WMS-G normal and WMS-G reverse= $p>0.308$ and $p >0.329$). Conclusion: Aerobic exercise has been found to potentially have beneficial effects on cognitive abilities in young adults, even after a single session. Clinicians in the field of cognitive rehabilitation may enhance treatment outcomes by incorporating aerobic activities into rehabilitation programs. Further studies with large sample groups and different types of aerobic exercises (swimming, running, etc.) are important to more clearly demonstrate the acute effects of aerobic exercises on cognitive functions.

Keywords: *Aerobic exercise, Cognitive function, Stroop test*

ÖZ

Amaç: Aerobik egzersizin kognitif fonksiyonlar üzerindeki etkileri iyi bilinmektedir, ancak aerobik egzersizin kognitif fonksiyonlar üzerindeki akut etkileri tam olarak anlaşılamamıştır. Bu çalışmada, sağlıklı genç yetişkinlerde 1 seans aerobik egzersizin bilişsel fonksiyonlar üzerindeki akut etkilerini araştırmayı amaçladık. Gereç ve Yöntemler: Çalışmaya 2020- 2022 yılları arasında Fizyoterapi ve Rehabilitasyon Fakültesi'nde öğrenim gören 52 sağlıklı genç yetişkin (24 erkek, 28 kadın) dâhil edildi. Katılımcılara Ergoline®-Ergoselect200 bisiklet ergometresi kullanılarak bir seans aerobik egzersiz yaptırılmıştır. Egzersiz rutini 5 dakikalık ısınma, ardından 20 dakikalık yüklenme ve 5 dakikalık soğuma periyodundan oluşmuştur. Katılımcıların dikkat düzeyleri Stroop Testi'yle, bellek düzeyleri Wechsler Bellek Ölçeği-Genelleştirilmiş Formunun (WBÖ-G) sayı dizisi (SD) alt testi ile değerlendirilmiştir. Değerlendirmeler egzersiz öncesi ve sonrası olmak üzere 2 kez yapılmıştır. Bulgular: Katılımcıların yaş ortalaması 23,34 ± 1,13 yıl olarak tespit edilmiştir. Katılımcıların Stroop Testi sürelerinde anlamlı iyileşme görülmüş ancak doğru ve hata sayılarında anlamlı bir fark oluşmamıştır. (Stroop 1, stroop 2, stroop 3, stroop 4 ve stroop 5= sırasıyla $p< 0,0001$, $p<0,008$, $p< 0,0001$, $p< 0,0001$ ve $p< 0,001$). Katılımcıların WBÖ-G değerlerinde anlamlı bir fark gözlenmemiştir (WBÖ-G normal ve WBÖ-G ters $p>0,308$ ve $p >0,329$). Sonuç: Aerobik egzersizin, tek bir seanstan sonra bile genç yetişkinlerde kognitif fonksiyonlar üzerinde olumlu etkileri olabilir. Koginitif becerilerin geliştirilmesinde, aerobik aktiviteler düşünülmeli ve egzersiz programlarına dâhil edilmelidir.Aerobik egzersizlerin kognitif fonksiyonlar üzerine akut etkilerini daha net farklı aerobik egzersiz türleri (yüzme, koşma vb.) ile daha fazla çalışma yapılması önem arz etmektedir.

Anahtar Kelimeler: *Akut, Aerobik egzersiz, Kognitif beceri, Stroop testi*

INTRODUCTION

Aerobic exercise is any physical activity that raises the heart rate and breathing volume to supply oxygen to the working muscles. Aerobic exercise is more convenient to perform and has a lower incidence of adverse effects as compared with drugs. Aerobic exercise is advised for at least 150 minutes per week and can be done at home with activities such as jumping rope, running, or aerobic strength circuits (1). The duration of aerobic exercise can start at 10 minutes and progress up to 60 minutes, depending on fitness level and goals (2). Aerobic exercise has multiple effects such as enhanced cardiovascular well-being, decreased blood pressure, improved emotional state, weight control, and a higher quality of sleep (3). Aerobic exercise provides numerous advantages for mental well-being, such as diminishing depression and anxiety, enhancing mood, and improving cognitive performance (4,5). Empirical studies have demonstrated that engaging in aerobic exercise diminishes symptoms in individuals afflicted with depression and anxiety (6). Additionally, it enhances physical fitness, potentially mitigating the development of these ailments. The mental advantages of aerobic exercise are rooted in neurochemical processes. It lowers the levels of stress hormones in the body and promotes the release of endorphins, which act as the body's innate pain relievers and mood enhancers (7). Moreover, studies have found that exercise reduces anxiety and despair, boosts self-esteem, and eases symptoms in individuals with severe mental illness (4).

Studies have shown that engaging in aerobic exercise can result in enhancements in multiple components of brain function, such as executive function, memory, and attention. Furthermore, aerobic exercise has been linked to the promotion of neurogenesis, which refers to the generation of new brain cells, as well as the mitigation of cognitive decline in elderly people. The cognitive benefits of aerobic exercise are believed to be associated with mechanisms such as enhanced cerebral blood flow, decreased inflammation, and the secretion of neuroprotective and growth factors. Hence, including consistent aerobic activity into one's daily regimen can enhance cognitive function and promote optimal brain health (8-11).

Numerous studies have demonstrated that participating in aerobic exercise has beneficial effects on brain functioning. Nevertheless, there is a lack of recognition of the immediate effects of aerobic exercise on cognitive function. While a limited number of studies in the literature have documented the immediate impact of aerobic exercise on cognitive functions, the results remain a subject of debate (12,13). According to Kamijo et al. (14) several studies indicate that engaging in moderate-intensity aerobic exercise has the potential to improve cognitive processes, whereas high-intensity exercise may have a detrimental effect on them. Nevertheless, alternative research has indicated that engaging in high-intensity aerobics can enhance cognitive function, contingent upon the temporal alignment between the cognitive task and the exercise (13). Our studies significance lies in its ability to illustrate the immediate effects of aerobic exercise on cognitive functioning, thereby addressing the existing gaps in the scholarly literature pertaining to this topic. The primary objective of our research was to examine the immediate impacts of aerobic exercise on cognitive abilities. We hypothesised that aerobic exercise would improve cognitive functions.

MATERIAL and METHOD

Study Design

This study involved 52 healthy young adults studying at Pamukkale University's Faculty of Physiotherapy and Rehabilitation between 2020 and 2022. The inclusion criteria were as follows: asemptomatic healthy adults, between the ages of 18 and 27, understood the purpose of the study. The exclusion criteria were as follows: young adults who had cardiac, pulmonary, physical, and psychological problems; young people whose use of drugs affected their cognitive and aerobic performance; and young people who had visual and hearing problems.

Participants

We calculated a total sample size of 45 with an effect size of 0.951, a power of 0.95, and an error probability of 0.05. We used G*Power 3.19 (Heinrich Heine University, Dusseldorf, Germany) for

the sample size calculations (15). We excluded 8 of the 60 participants because they did not meet the inclusion criteria of the study. We completed the study with 52 participants.

Outcome Measurements

We recorded the demographic characteristics of the participants on a demographic data form that we created beforehand. We assessed the participants' attention levels using the Stroop Test pre and post aerobic exercise. Additionally, we examined the participants' memory using the number sequence (SD) subtest of the Wechsler Memory Scale-Generalized Form (WMS-G).

The Stroop Colour and Word Test (SCWT) was used to assess an individual's executive processing abilities, selective attention capacity, and processing speed. This test, which consists of five different cards, requires participants to complete the given task as quickly as possible, recording their time in seconds. The tasks on the cards were as follows: 1. Reading the colour names written in black pen on the card (e.g., black, blue, red); 2. Reading the colour names printed in colour on the card; 3. Saying the colours of the shapes printed in colour on the card; 4. Saying the colour of a word coloured but not written on the card; 5. Saying the colour of a word whose colour name is written on the card but whose colour may differ. At the end of the test, we recorded the completion time, the number of errors made, and the number of corrections (16).

The Wechsler Memory Scale-Generalized Form (WMS-G) was employed to evaluate the participant's memory level. VMS has the capacity to assess various memory functions, including auditory memory, visual memory, visual working memory, immediate memory, and delayed memory, in individuals aged between 16 and 90. We used digital span subtest of VMS-G to assess memory functions. In this subtest, the individual is presented with a consecutive sequence of numbers and instructed to count them in the same sequence. Subsequently, a consecutive sequence of numbers is presented to the individual, who is then instructed to enumerate the numbers in reverse. Digit span subtest consists of 16 numbers, 8 straight number sequences and 8 reversed number sequences. The VMS-G digital span subtest has shown excellent reliability in individuals aged between 21 and 30 (Cronbhach's alpha: 0.88) (17,18).

Procedure

A total of 52 individuals engaged in aerobic exercise using the Ergoline®-Ergoselect200 bicycle ergometer. The exercise routine consisted of a 5-minute warm-up, followed by a 20-minute loading period, and concluded with a 5-minute cool-down (12,19).

Throughout the exercise, participants maintained a heart rate that did not surpass 60–70% of their maximum heart rate. We conducted a pre-exercise assessment session and a 2-minute post-exercise session. We calculated the maximum heart rate as 220 minus the participant's age (20).

Statistical Analysis

Collected data were processed using SPSS version 23.0 (IBM Corp., Armonk, NY, 227 USA) for Windows. The normalities of data distributions were assessed using the Kolmogorow Smirnow test ($p<0.05$), skewness, and kurtosis values. The Paired Simple test was used for parametric variables to asses within group differences, and results are expressed as mean, standart deviations, minumum-maximum. The Wilcoxon's signed-rank test was performed for non-parametric variables to analyze within-group differences, and results are expressed as medians, minumum and maximum. The level of significance was set at $p<0.05$.

RESULTS

This study included 52 young adults (24 males and 28 females). (46.2 % males /53.8% females). The mean age of the participants was 23.34 ± 1.13 years. Body mass index (BMI) of participants were found 22.50 ± 2.95 kg/m2 (Table 1).

Table 1: Demographic Values of Participants,

	X± sd	Min – Max
Age (year)	23.34±1.13	20-27
Height (cm)	171±9.18	155-187
Weight (kg)	65.1±14.5	35-97
BMI (kg/m^2)	22.5±2.95	16.60-29.90
Gender(male/female)	24/28	-
Gender (%)	(46.2% / 53.8%)	

X: Mean, sd: Standart deviations, Min-Max: Minimum - Maximum, cm: Santimeter, kg: Kilogramme, BMI: Body mass index, kg/m^2: Kilogramme /meter square, %: Percentage.

Participants completed the stroop 1 test in 8.11 seconds before aerobic exercise. After the aerobic exercise, the completion time decreased to 7.37 seconds. There was a significant difference in stropp 1 test times between pre- and post-exercise values (p: 0.0001, Table 2).

Participants completed the stroop 2 test in 8.89 seconds before aerobic exercise. After the aerobic exercise, the completion time decreased to 7.78 seconds. There was a significant difference in stropp 2 test times between pre- and post-exercise values (p: 0.008, Table 2).

Participants completed the stroop 3 test in 10.9 seconds before aerobic exercise. After the aerobic exercise, the completion time decreased to 9.32 seconds. There was a significant difference in stropp 3 test times between pre- and post-exercise values (p: 0.0001, Table 2).

Participants completed the stroop 4 test in 12.0 seconds before aerobic exercise. After the aerobic exercise, the completion time decreased to 10.9 seconds. There was a significant difference in stropp 4 test times between pre- and post-exercise values (p: 0.0001, Table 2).

Participants completed the stroop 5 test in 18.0 seconds before aerobic exercise. After the aerobic exercise, the completion time decreased to se16.2 seconds. There was a significant difference in stropp 5 test times between pre- and post-exercise values (p: 0.001, Table 2).

The participants showed no nosignificant improvement in stroop test number of corrects and errors (Stroop 1, stroop 2, stroop 3, stroop 4, and stroop 5= $p>0.05$) (Table 2).

The participant showed no significant improvement in WMS-G values (WMS-G normal and WMS-G reverse= p:0.308 and p:0.329) (Table 2).

Table 2: Comparison of Pre and Post Aerobic Exercise Values of Stroop and WMS-G Test.

		Pre exercise Median (Min – Max)	Post exercise Median (Min – Max)	w	P
Stroop 1	**Time (second)**	8.11 (5.20 – 10.91)	7.37 (5.03 – 9.56)	1202	**0.0001***
	Number of errors	0. (0 - 0)	0. (0 - 1)	0.	1.00
	Number of correct	0. (0 - 1)	0. (0 - 0)	3.00	0.346
Stroop 2	**Time (second)**	8.89 (8.68 – 19.71)	7.78 (8.09– 14.18)	978.5	**0.008***
	Number of errors	0. (0 - 0)	0. (0 - 0)	0.	-
	Number of correct	80. (0 - 1)	0. (0 - 2)	20.0	0.236
Stroop 3	**Time (second)**	10.9 (7.0 – 15.08)	9.32 (7.0-14.99)	1273	**0.0001***
	Number of errors	0. (0 - 1)	0. (0 - 2)	0.	1.00
	Number of correct	0. (0 - 4)	0. (0 - 2)	51.5	0.685
Stroop 4	**Time (second)**	12.0 (8.68-19.71)	10.9 (8.09 – 14.71)	1288	**0.0001***
	Number of errors	0. (0 - 0)	0. (0 - 1)	1.50	0.586
	Number of correct	0. (0 - 2)	0. (0 - 3)	71.5	0.05
Stroop 5	**Time (second)**	18.0 (10.56 – 31.09)	16.2 (8.9 – 22.27)	1059	**0.001***
	Number of errors	0. (0 - 2)	0. (0 - 3)	21.5	0.951
	Number of correct	0. (0 - 5)	0. (0 - 2)	197	0.329
WMS-G	**WMS-G normal**	5.50 (4 - 8)	6.00 (3 - 8)	271	0.308
	WMS-G reverse	5.00 (3 - 7)	5.00 (3 - 7)	203	0.372

Memory Scale-Generalized, *p < 0.05
X: mean, SD: Standard deviation, Min-Max: Minimum - Maximum, w: Wilcoxon test statistics, WMS-G:Wechsler

DISCUSSION and CONCLUSION

The primary goal of the present research was to examine the immediate effects of aerobic exercise on cognitive functions in young adults. A notable enhancement in the cognitive abilities of young adults was demonstrated subsequent to a solitary session. The cognitive performance of adults may be enhanced by engaging in moderate-intensity aerobic exercise, whereas high-intensity exercise has the potential to hinder it. Nevertheless, alternative research has indicated that cognitive function can be enhanced with high-intensity exercise, contingent upon the temporal alignment between the cognitive activity and the exercise (12,13).

The literature extensively documents the impact of prolonged aerobic exercise on cognitive functioning (21, 22). Nevertheless, the comprehensive awareness of the immediate impacts of aerobic exercise on cognitive functions remains insufficient owing to variations in parameters such as intensity of exercise, duration, and intensity, as well as its utilisation across diverse age cohorts and in relation to various medical conditions (12,13). In a study involving 12 elderly and 12 young males, Komijo et al. examined the short-term impacts of aerobic exercise on cognitive performance. They observed that the latent phase of P3, which is believed to reflect the brain activity involved in maintaining working memory during updates to the mental model of the stimulus environment, increased during both light and moderate aerobic exercise in both age groups. However, the amplitude of P3 only increased in the young adult group following moderate aerobic exercise. Furthermore, both groups experienced significant improvements in reaction time following moderate exercise (14).

In order to examine the impact of aerobic exercise on cognitive function, a cross-over study was conducted on a group of 20 patients diagnosed with Parkinson's disease. These participants

underwent training on a recumbent bicycle ergometer known as the 700 Excite + Recline, provided by Technogym USA©, which is located in Seattle, Washington. Subsequently, these individuals were enrolled in a specific aerobic exercise programme that involved performing the exercises at an intensity level of 50% heart rate reserve (HRR) for a duration of 20 minutes. Participants in both the exercise and control conditions showed a reduction in decision-reaction time, according to the study by Silveira and Roy Also, this study found that participants had a slower decision reaction time for the target stimulus in comparison to non-target stimuli, regardless of the time or experiment (23).
A study has examined the acute effects of moderate exercise on cognitive functions, specifically the Stroop test. According to this study short periods of moderate exercise can enhance activity in the dorsolateral prefrontal cortex, a brain region associated with executive functions, and enhance cognitive performance on tests such as the Stroop test (24). This is achieved by boosting the activation of brain regions involved in cognitive control and goal-directed behavior, such as the left dorsolateral prefrontal cortex. In parallel with the above-mentioned studies, our results have shown significant improvement in Stroop test times. These results showed that aerobic exercise, even for one session, may be effective on cognitive functions. We bring these findings to the attention of specialists working in neurorehabilitation, cognitive rehabilitation, and sports rehabilitation.

Engaging in intense aerobic exercise has been found to have immediate positive effects on memory functioning. Research has shown that engaging in one session of moderate-intensity aerobic exercise can improve working memory (25) and the ability to differentiate between similar memories, declarative memory, and procedural memory (26). The results indicate that engaging in intense aerobic exercise can have a beneficial effect on tasks related to memory, emphasising the potential of exercise as a non-pharmacological approach to improve memory function in people of various age groups (27,28). In our study, we observed a slight improvement in memory capacity, but it was not statistically significant. We believe that the duration and intensity of exercise may play a role in this.

Due to the limited quantity and heterogeneity of studies examining the immediate impact of aerobic exercise on cognitive functions, further research is required in this domain. Our study observed enhancements in cognitive functions that align with the aforementioned literature. Consequently, our study will contribute to the expanding body of research in this particular field.

Naturally, our study had some limitations. We conducted our study solely on healthy individuals, underscoring the importance of studies involving individuals with cognitive impairments. Furthermore, our study did not incorporate any form of grouping or randomization. Furthermore, our study did not incorporate any form of grouping or randomization.

In improving cognitive skills, the integration of aerobic exercises into the program may contribute to the development of these skills. With the goal to acquire more understanding of the immediate impacts of aerobic exercise, a variety of aerobic exercise types—such as running and swimming—is necessary.

Declaration of Ethical Code: The present study obtained approval from the Non-Interventional Clinical Research Ethics Committee at Pamukkale University (Ethics number: 60116787-020/15169). Before participating in the study, all participants were required to give written consent after receiving comprehensive information about the study protocol, which was in accordance with the ethical principles outlined in the Declaration of Helsinki for human experimentation.

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A Comparison of the Touwen Infant Neurological Examination, General Movement Assessment and Alberta Infant Motor Scale in Infants Born Preterm

Prematüre Bebeklerde Touwen İnfant Nörolojik Değerlendirmesi, General Movements Değerlendirmesi ve Alberta İnfant Skalasının Karşılaştırılması

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ABSTRACT

Objective: Infants born preterm are known to be at risk of moderate to severe developmental problems. The study aimed to compare Touwen Infant Neurologic Examination (TINE), General Movement Assessment (GMA) and Alberta Infant Motor Scale (AIMS) scores assessed on the same day at 3-to-5 months-of-corrected-age in infants separated by gestational week. Materials and Methods: We included a total of 78 infants with a history of preterm birth, as very preterm (<32 weeks, n = 26), moderate preterm ($32^{0/7}$ to $33^{6/7}$ weeks, n = 30) and late preterm ($34^{0/7}$ to $36^{6/7}$ weeks, n = 22), at 3 to 5 months-of-corrected-age. The study compared the results of TINE, AIMS and GMA in preterm infants separated by gestational age, and analysed AIMS scores according to GMA results. In addition the association between TINE and AIMS scores was assessed. Results: There was statistical significance between the prone motor performances of the groups, due to the statistical difference between infants born late preterm and infants born very preterm; the prone motor performance of infants born late preterm was significantly higher than infants born very preterm. Infants with normal fidgety movements had higher prone (p=0.043) and supine (p= 0.037) motor performance scores than infants with aberrant fidgety movements. A significant negative low correlation was found between TINE findings and total AIMS scores. Conclusions: Infants with absent and abnormal fidgety movements have lower AIMS score and gestational age might affect AIMS score. Additionally, it has been showed that abnormal neurologic findings, according to TINE, are negatively related to AIMS score.

Keywords: *General movements, Minor Neurological Dysfunction, Preterm*

ÖZ

Amaç: Prematüre bebeklerin orta ila ciddi gelişimsel sorunlar açısından risk altında olduğu bilinmektedir. Çalışmanın amacı, gestasyonel yaşlarına göre ayrılan prematüre bebeklerin düzeltilmiş 3 ila 5 aylık iken aynı gün içerisinde değerlendirilen Touwen İnfant Nörolojik Değerlendirmesi (TİND), General Movement Değerlendirmesi (GMs) ve Alberta İnfant Motor Skalası (AİMS) skorlarını karşılaştırmaktır.

Materyal ve Metot: 3-5 ay düzeltilmiş yaşlarında gestasyonel yaşlarına göre erken prematüre (<32 hafta, n = 26), orta prematüre ($32^{0/7}$ ila $33^{6/7}$ hafta, n = 30) ve geç prematüre ($34^{0/7}$ ila $36^{6/7}$ hafta, n = 22) olmak üzere toplam 78 prematüre bebek çalışmaya dahil edilmiştir. Çalışmada gestasyonel yaşa göre ayrılan prematüre bebekler arasında TİND, AİMS ve GMs değerlendirmesi sonuçları karşılaştırılmış ve GMs sonuçlarına göre AİMS skorları incelenmiştir. Ayrıca TİND ve AİMS skorları arasındaki ilişki de değerlendirilmiştir. Bulgular: AİMS sonuçlarına göre; grupların yüzüstü motor performansları arasında geç prematüre bebekler ile erken prematüre bebeklerden kaynaklanan bir fark bulundu; geç prematüre bebeklerin yüzüstü motor performansı erken prematüre bebeklerden daha yüksekti. GMs değerlendirmesine göre; normal *fidgety* hareketleri görülen bebeklerin AİMS'ten aldıkları yüzüstü (p=0,043) ve sırtüstü (p= 0,037) motor performans skorları, anormal *fidgety* hareketleri görülen bebeklerden daha yüksekti. TİND ile toplam AİMS skorları arasında negatif düşük bir korelasyon bulundu. Sonuç: Sonuç olarak, *fidgety* hareketleri görülmeyen ya da anormal olan prematüre bebeklerin AİMS skoru yani motor performanslarının daha kötü olduğu ve gestasyonel yaşın AİMS skorunu etkileyebileceği görüldü. Ayrıca, TİND'a göre anormal nörolojik bulgular arttıkça AİMS skorunun düştüğü bulundu.

Anahtar Kelimeler: *General movements değerlendirmesi, Minör nörolojik disfonksiyon, Prematüre*

INTRODUCTION

Preterm birth, which is defined by the World Health Organization (WHO) as birth before 37 gestational weeks or 259 days, is a main indicator of morbidity and mortality in the newborn, and can have long-term adverse effects on infant health (1). Complications of preterm birth are the leading cause of death in children under 5 years of age. In 2014, preterm birth was estimated to affect 10.6% of all births globally, and it was reported that preterm birth rates ranged from 5% to 18% across 184 countries (2, 3). Although there are various classifications related to preterm birth, the general classification is extremely preterm (<28 weeks), very preterm ($28^{0/7}$ to $31^{6/7}$ weeks), moderate preterm ($32^{0/7}$ to $33^{6/7}$ weeks), and late preterm ($34^{0/7}$ to $36^{6/7}$ weeks) (4). The rates of morbidities such as low birthweight, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, and associated morbidities are seen at higher rates in infants born preterm than term infants (5-6). In addition, 50% of these infants have the risk of future motor coordination problems, cognitive disorders, attention deficits, and minor neurological dysfunction (MND), and 5-15% have a high risk of cerebral palsy (CP) (4, 7).

Neurological symptoms which emerge in the absence of evident neurological pathology are defined as MND and have been reported as being seen at a much higher rate in preterm infants (8). Delayed development of fine and gross motor skills, permanent neuromotor abnormalities, speech problems, intellectual delay, attention-deficit hyperactivity disorder, and learning problems which lower academic success are seen in children associated with MND (9). It is difficult to diagnose MND during early infancy, and a diagnosis of MND is often not made until preschool age. The study of Hadders Algra et al. (10) concluded that MND could be determined reliably during infancy with the Touwen Infant Neurologic Examination (TINE) and the presence of MND in infancy is a risk for developmental dysfunction in later life and highlights the need for careful follow-up. TINE is not widely used in clinical and research studies; however, earliest diagnosis of children with MND may provide early intervention for improving functional developmental outcomes (10).

The aim of this study was to compare motor and neurologic outcome assessed on the same day at 3 to 5 months-of-corrected-age in infants born preterm at three different gestational age (GA) periods on three standardized assessments; TINE, General Movement Assessment (GMA) and Alberta Infant Motor Scale (AIMS). In consideration of the extant literature, our hypothesis was that GA may influence both gross motor and neurological outcomes, as well as early motor performance, in premature infants. The aforementioned three assessments were selected to assess different aspects of development, and the research questions were established; (i) Are there differences in the motor and neurological outcome of preterm infants born at different GA? (ii) Is there a difference between the motor performances of preterm infants according to GMA analysis (normal and abnormal)? (iii) Are the neurological status (TINE) and motor performance (AIMS) of preterm infants related?

MATERIAL and METHOD

Participants

The study was conducted in the Developmental and Early Physiotherapy Unit of Hacettepe University, between February 2018 and December 2019, and it was approved by the Non-Interventional Clinical Research Ethics Committee of Hacettepe University (decision no: GO18/149, dated:06/02/2018). Criteria for inclusion were a GA of less than 37 weeks and a corrected age of 3-5 months. The exclusion criteria included infants with chromosome malformations, malignant disorders, or congenital syndrome whose families did not want to participate in the study and infants with a history of periventricular leukomalacia (PVL), hypoxic-ischemic encephalopathy (HİE), and intraventricular hemorrhage (IVH). Written informed consent for participation in the study was obtained from the parents of all the infants. The preterm infants at a corrected age of 3-5 months were included and classified according to GA as very preterm (VPT): <32 weeks, moderate preterm (MPT): $32^{0/7}$ to $33^{6/7}$ weeks, and late preterm (LPT): $34^{0/7}$ to $36^{6/7}$ weeks. The study included a total of 78 infants born at different GA periods; 26 in the VPT group,

30 in the MPT group, and 22 in the LPT group. The mean birth weight and assessment age of the infants were 1827 g and 14.2 weeks, respectively. The infant and mother data are presented in Table I.

Procedure

We conducted a prospective study of preterm infants born at different GA between a corrected age of 3 to 5 months old. As soon as the infant came to our clinic, first GMA was recorded (5-10 minutes) and then TINE (15-20 minutes) and AIMS (20-30 minutes) assessments were performed, respectively with resting periods in between. The video recordings for GMA were performed during periods of active wakefulness of the infant with the infants lying in a supine position and partly dressed without crying or fussing. The infants were then assessed using TINE and AIMS. All assessments were performed on the same day. Assessors were experienced paediatric physiotherapists, who were blind to the infant's clinical history.

Touwen Infant Neurological Examination (TINE)

The TINE was used to assess the neurological status of the infants. The assessment is made by observing the infant when awake and calm, in prone, supine and sitting positions, and motor behaviours when reaching and grasping. TINE is one of the standardized infant neurological assessments with good psychometric properties, including good reliability in a sample of infants aged 3 to 12 months (inter-assessor agreement k = 0.83, 95% CI 0.68-0.99) (10). The findings of the TINE were classified according to age-specific norms into clusters of dysfunction as follows: (i) dysfunctional reaching and grasping (goal directed motility arms, type of grasping, delayed development of grasping, arm/hand posture during reaching and grasping, quality of reaching motility etc.); (ii) dysfunctional gross motor function (tremor, head balance, motility in supine and prone position, performance at pull-to-sit manoeuvre, etc.); (iii) signs of brainstem dysfunction (dysfunctional glabella and masseter reflex, Doll's eye phenomenon and Moro reaction, etc.); (iv) visuomotor dysfunction (deviant fixation of eyes and eye movements, visual pursuit, strabism, sunset, etc.); and (v) sensorimotor dysfunction (deviant muscle tone, regulation of tendon reflexes, foot sole response, etc.). The total number of dysfunctional clusters is calculated in order to determine the neurological function classification. The classifications are as follows: normal, normal sub-optimal, minor neurological dysfunction, or abnormal (The score range is 0–3 respectively, with 0 indicating normal function). The TINE administration took 15-20 minutes. The assessor (D.P. and M.A.) first learned the TINE procedure, and then practiced to gain experience (at least 50 assessments) and to learn the distinction between 'typical' and 'sign of MND' as reported by Hadders-Algra et al. (10). TINE was conducted on all infants included in the study.

General Movements Assessments

GMA is one of the most predictive tools for detecting an infant's later neurodevelopmental outcome, particularly CP, before 5 months of corrected age (11). The excellent predictive power of GMA, especially in a population at high risk of CP, is mainly based on fidgety movements with sensitivity values from 95% to 98% and specificity values from 89% to 96% (11, 12). As a part of GMA, fidgety movements are continuous small amplitude, moderate speed movements of shoulders, wrists, hips, and ankles in all directions and of variable accelerations in typically developing infants at 3–5 months post-term age (13). In the assessment, fidgety movements were examined and scored as present and normal (F+), absent (F-) and abnormal (AF) (13). Seven video recordings for GMA could not be performed as the infant was irritable or sleepy: 3 in infants born VPT, 3 in infants born MPT, and 1 in infants born LPT. The video recordings were assessed by A.M. and H.A., who are GMA certified and experienced paediatric physiotherapists blinded to the infants' clinical histories. Inter-assessor Cohen's kappa coefficient for GMA was statistically significant and showed high agreement ($\kappa = 0.93$, $p < 0.001$).

Alberta Infant Motor Scale (AIMS)

Gross motor performance of infants assessed with the AIMS, which is a norm-referenced tool with high predictive validity for long-term motor outcomes and excellent intrarater- interrater reliability in children born preterm (14). The movements of the infant are observed when supine, prone, sitting, and standing. The components tested for each item are based on 3 elements of movement: weight bearing, posture, and antigravity movements. The last and the most mature items are identified in every position, these two items constitute the developmental "window" and then score every item in the "window" as "observed" (1 point) or "not observed (0 points). The sum of all items observed gives a total raw AIMS score ranging from 0 to 58 and the total points are converted to age-based centile values. Scores are marked on the AIMS forms, which consist of 58 items in 4 subscales. High percentile ranks indicate the maturity of the infant's gross motor skills. Infants with a centile score of ≤5 are assessed as abnormal. Since "sitting" and "standing" positions are beyond the motor development of infants at a corrected age of 3-5 months, the infant was held in that position by the assessor and observed as follows: weight-bearing on the feet, the position of the head, active control of the trunk, and variable movements of the legs according to gravity (14, 15). An assessor (D.P.) performed the assessment and it took about 20 minutes. AIMS was conducted on all infants included in the study.

Data Analysis

Statistical analyses were performed using SPSS software version 24 (IBM ®, Armonk, NY, USA). To achieve 80% power to detect a difference with 95% confidence using a two-tailed test, based on effect size of d=0.392 (16), a sample size of 25 participants was required for each group. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. One-way ANOVA was used to compare AIMS scores among groups (VPT, MPT, LPT) and if at least one of the groups did not show normal distribution, the Kruskal Wallis test was used. Post-hoc corrections were used when there was a difference between the AIMS scores of VPT, MPT, and LPT infants. The Chi-Square test was used to compare TINE and GMA proportions in different groups. Independent sample t-tests were used to compare AIMS scores according to GMA groups (F+/(F-and AF)), and when at least one group did not show normal distribution, the Mann Whitney U-test was used. Finally, while investigating the associations between TINE and AIMS scores, the correlation coefficients and their significance were calculated using the Spearman rank order correlation. According to the correlation coefficient, correlations were interpreted as 0.05-0.4: low correlation, 0.4-0.7: moderate correlation, and 0.7-1.0: strong correlation (17).

RESULTS

The baseline data on the characteristics and risk factors of the infants are given in Table I. Of those included in the study, 5.1% were categorized as MND on the TINE and 11.3% (8.5% absent and 2.8% abnormal) showed aberrant (absent or abnormal) fidgety movements on GMA (Table I).

Table 1: Characteristics and Risk Factors of Infants

		Mean (SD)	(Min-Max) (n=78)
Birth weight (gr)		1827 (660.2)	730-3200
Height (cm)		61 (3.9)	52-70
Birth weight (gr)		1827 (660.2)	730-3200
Assessment age (week)/n=78		14.2 (2.1)	12-20
Assessment age (week)	Very preterm	14 (2)	12-20
	Moderate preterm	14.4 (2)	12-20
	Late Preterm	14.5 (2.2)	12-18
Gestational age (week)	Very preterm	28.7 (1.6)	25-31
	Moderate preterm	33.0 (0.9)	32-34
	Late Preterm	36.0 (0.8)	35-36
		n	**(%)**
Gender	Male	41	(52.6)
	Female	37	(47.4)
Risk Factors	Respiratory Distress Syndrome	3	(3.8)
	Bronchopulmonary Dysplasia	1	(1.3)
	Patent Ductus Arteriosus	2	(2.6)
	Necrotizing Enterocolitis	1	(1.3)
	Periventricular Leukomalacia	0	(0)
	Intraventricular Haemorrhage	0	(0)
Maternal Illness During Pregnancy	Pre-eclampsia	13	(16.7)
	Gestational Diabetes	6	(7.7)
	Hyperbilirubinemia	10	(12.8)
Type of Birth	NVB	10	(12.8)
	C/S	68	(87.2)
Type of Pregnancy	N	57	(73.0)
	IVF	21	(27.0)
Multiple Gestation	Single	41	(52.5)
	Twins	33	(42.3)
	Triplets	3	(5.2)
AIMS Total Score		9.1 (3.6)	NA
GMA	F+	63	(88.7)
	F-	6	(8.5)
	AF	2	(2.8)
TINE	Neurologically normal	42	(53.8)
	Sub-optimal, i.e. 1-2 Dysfunctional Clusters	30	(38.5)
	MND, i.e. > 2 Dysfunctional Clusters	4	(5.1)
	Abnormal, i.e. Clear Neurological Syndrome	2	(2.6)

AF; Abnormal fidgety, F-; Absent fidgety, F+; Normal fidgety, C/S; cesarean section, GMA; General Movement Assessment, IVF; in vitro fertilization, MND: minor neurologic dysfunction, N; normal, NVB; normal vaginal birth, NA = Not applicable, SD; standard deviation, TINE; Touwen Infant Neurological Examination.

The comparisons outcomes of TINE of the infants and the results of GMA according to GA are shown in Table II. According to TINE, there was no significant difference between the groups ($p>0.05$). Of all infants, 53.8% of infants born VPT, 33.3% of infants born MPT and 54.5% of infants born LPT were scored suboptimal to abnormal on the TINE. According to GMA, there were 8 infants with aberrant fidgety movements; 4 out of 23 (17.4%) in the VPT group, 2 out of 27 (7.4%) in the MPT group and 2 out of 21 (9.5%) in the LPT group.

Table 2: Comparison Of The TINE And GMA Of The Infants Included In The Study According To The Gestational Ages At Birth

		Gestational Age			X^2	p
		Very preterm <32 wk	Moderate preterm 32-34 wk	Late preterm >34 wk		
		n (%)	n (%)	n (%)		
TOUWEN	Neurologically normal	12 (46.2)	20 (66.7)	10 (45.5)	3.22	0.19
	Suboptimal/MND or Abnormal	14 (53.8)	10 (33.3)	12 (54.5)		
GMA	F+	19 (82,6)	25 (92,6)	19 (90,5)	2.33	0.67
	F- / AF	4 (17,4)	2 (7,4)	2 (9,5)		

X^2; Chi-Square test, AF; Abnormal fidgety, F-; Absent fidgety, F+; Normal fidgety, GMA; General Movement Assessment, wk: weeks

The comparisons of the AIMS scores of the infants according to GA are shown in Table III. At prone position, the mean values of the AIMS raw scores were significantly higher in infants born LPT than that of the other groups ($p<0.01$). No significant difference was determined between the groups in respect of the mean raw values of the AIMS subcategories and the AIMS centile scores ($p>0.05$) (Table III).

Table 3: Comparison of The AIMS Scores of The Infants In Corrected 3 To 5 Months According To The Gestational Ages At Birth

	Gestational Age at Birth						F	p	Post-Hoc
	Very preterm <32 wk (n=26)		Moderate preterm 32-34 wk (n=30)		Late preterm >34 wk (n=22)				
	Mean	SD	Mean	SD	Mean	SD			
AIMS total	8.5	3.4	9.3	3.1	9.5	4.5	0.51	0.598	
AIMS prone	2.2	1.1	3.2	1.6	3.6	2.3	4.11	**0.020***	<32 wk->34 wk
AIMS supine	3.4	1.6	3.5	1.3	3.6	1.8	0.05	0.944	
AIMS sitting	1.7	1.0	1.6	0.9	1.3	.8	1.62	0.205	
AIMS standing	1.2	1.0	1.1	0.4	1.0	0.5	0.73	0.481	
	Median (%25-75 IQR)		Median (%25-75 IQR)		Median (%25-75 IQR)		X^2	p	
AIMS centile scores	10 (0-25)		10 (5-25)		10 (0-10)		1.06	0.58	

F; One-way ANOVA, X^2; Kruskal Wallis, AIMS; Alberta Infant Motor Scale, SD; standard deviation, IQR; Interquartile Range,*p <0.05, wk: weeks

Comparison of the AIMS scores of the infants according to GMA statistics are shown in Table IV. Statistical significance was found in favor of infants with normal fidgety movements for the "prone" and "supine" subparameters ($p<0.05$). No statistical significance was found for the other sub-parameters ($p>0.05$).

Table 4: Comparison of The AIMS Scores of The Infants According To GMA Characteristics

	GMA					
	F+ (n=63)		F- and AF (n=8)		t	p
	Mean	SD	Mean	SD		
AIMS total	9.4	3.5	7.6	4.1	1.69	0.095
AIMS prone	3.1	1.8	2.7	1.6	0.78	**0.043***
AIMS supine	3.7	1.4	2.7	1.9	2.12	**0.037***
AIMS sitting	1.6	0.9	1.1	0.9	1.82	0.072
AIMS standing	1.1	0.7	1.1	0.6	0.12	0.903
	Median (%25-75 IQR)		Median (%25-75 IQR)		Z	p
AIMS centile scores	10 (0-25)		0 (0-10)		-1.87	0.061

t;Independent sample t test, Z;Mann-Whitney U test, AIMS; Alberta Infant Motor Scale, GMA; General Movements Assessment, F-; Absent fidgety, AF; Abnormal fidgety, F+; Normal fidgety, SD; standard deviation, IQR; Interquartile Range.

The relationship between the TINE and AIMS scores of the infants are shown in Table V. A negative, low-level statistically signficant correlation was determined between the TINE and the total, prone, supine, sitting, and centile values of the AIMS ($p<0.05$).

Table V. The Relationship Between TINE and AIMS Scores of The Infants Included In The Study

	TINE	
	r	p
AIMS total	-0.33	**<0.001****
AIMS prone	-0.25	**0.002***
AIMS supine	-0.32	**<0.001****
AIMS sitting	-0.25	**0.002***
AIMS standing	-0.07	0.490
AIMS centile scores	-0.29	**0.001***

AIMS; Alberta Infant Motor Scale, r; Spearman correlation test,*p <0.05, **p <0.01

DISCUSSION and CONCLUSION

The current study compared the motor and neurologic outcomes of infants born preterm at 3 to 5 months-of-corrected-age according to GA with three different assessments -TINE, GMA, and AIMS- that were performed on the same day. The results demonstrated that the infants born LPT had better motor performance than the infants born VPT. Assessment of neurologic and motor outcomes according to TINE and GMA showed no difference between groups. In addition, aberrant fidgety movements and worse neurological scores on TINE were associated with worse AIMS performance.

To the best of our knowledge, no study exist which used TINE, GMA, and AIMS together on the same time, in fidgety periods at a corrected age of 3-5 months. Only one study by Olsen et al. (18) also used those three assessments and Neurological, Sensory, Motor, Developmental Assessment (NSMDA), in which they associated GMA in the preterm and term period with the neurodevelopmental outcome assessed by TINE and AIMS at 12 months-of-corrected-age for infants born VPT. They (18) reported that abnormal GMA quality in the preterm and term periods was associated with adverse TINE and AIMS scores at a corrected age of 12 months.

The neurological condition in infancy is prone to change due to the developmental transformations of the infant brain (19). If the infant does not have a clear neurological dysfunction, early prediction is best when it is based on multiple assessments (10). There is scant evidence and research about the concept of MND in infancy. However, Hadders Algra et al. (10) reported that MND can be assessed reliably during infancy with the TINE and with good psychometric properties, including a good inter-assessor reliability. A relationship between preterm birth and MND seen in infancy has been shown in previous studies (10, 20). It is reported that as comorbidities increase when GA decreases, the rate of MND also increases (10, 20). Hsu et al. (20) in a cohort with 151 infants born preterm found that the proportion of MND at a corrected age of 6 months was 21.6% for infants born before 28 weeks, 13.2% for 29 to 32 weeks and 8.2% for 33 to 36 weeks. The present study revealed that the TINE scores were comparable between the groups separated by GA. Our expectation was that the rate of MND in infants born VPT was higher than in infants born MPT and LPT. However, this finding may be attributed to the low neurological risk and low neonatal morbidity rate observed in the VPT group included in this study.

It was shown in studies (21-23) that infants born preterm were more likely to have abnormal GMA as well as a poorer quality of early motor repertoire than infants born at term. In our study we compared the GMA results of infants born preterm according to GA and the findings were similar between groups. This can be explained by the fact that our study population, including infants in the VPT group, consisted of relatively low-risk infants and therefore there was no difference between the groups. Additionally, previous studies (21-23) generally compare the GMA results of infants born VPT and infants born at term. In our study, we compared infants born at VPT, MPT, and MPT among themselves. Therefore, we could not compare the outcomes we found in our study with the studies that included moderate and late preterm infants.

We found that our group of infants born preterm had a high percentage of aberrant fidgety movements (11,3%, n=8/78). This percentage is rather high compared to findings of Salavati et al. (22) (9.4%) in infants born VPT and Peyton et al. (24) (6%) in infants born MLP at 32-36 weeks gestation with no risk factors. However Yardımcı-Lokmanoğlu et al. (25) reported that 18.1% of the infants born preterm (GA between 23 and 36 weeks) showed aberrant fidgety movements and Zang et al. (26) stated that 23% of preterm infants born ≤34 weeks displayed aberrant fidgety movements. The varying rates of aberrant fidgety movements observed in these studies conducted in countries with disparate socioeconomic levels may be attributed to the presence of additional risk factors beyond prematurity. Furhermore, the high percentage of aberrant fidgety movements observed in our study may be indicative of potential neurodevelopmental issues, necessitating long-term follow-up to ascertain the long-term outcomes.

As GA and birthweight decrease, the rate of neurodevelopmental problems in the infants increases (27, 28). Infants born at <32 weeks and with a birthweight of <1500g are at notably higher risk (28, 29). In a systematic review by Fuentefria et al. (30), it was reported that differences were seen in the gross motor performances of preterm and full-term infants at different ages, and a relationship was noted between atypical motor performance in AIMS and risk factors such as prematurity-related low birthweight, peri-intraventricular hemorrhage, and chronic lung disease. In the current study, except for the AIMS prone scores, the motor performances of the groups were similar. The prone motor performance was higher in infants born at $34^{0/7}$ to $36^{6/7}$ weeks than infants born at <32 weeks. Consistent with these findings, Pin et al. (31) reported that delayed motor development became more evident with progression from the 4th month to the 8th month in preterm infants compared to term infants. Other studies by Van Haastert et al. (32) and Syrengelas et al. (33) reported that the AIMS scores of preterm infants were lower than full term infants at all age levels. In a study by Valentini et al. (34) it was found that preterm infants had higher scores in supine and standing postures in the first trimester of life compared with full term infants, but in the following months the full term infants had more proficient movements in demanding postures. Combined with ours, these results demonstrate the variability of movement patterns in preterm infants. But the most important point

that distinguishes our study from those above was that we compared preterm infants among themselves according to their GA. The possible explanation of higher scores in a prone position in infants born LPT stem from the hypotonia observed in infants born VPT (35) Less prone positioning of the preterm infants and more time spent in neonatal intensive care units for medical treatment may negatively affect the acquisition of movements in supine and prone posture or bring higher rates of neonatal complications than the other groups.

It was also reported that the abnormal GMA of infants born at <32 weeks GA were associated with worse AIMS motor scores at 12 months corrected age (18). In the study of Snider et al. (36), which investigated the construct validity of GMA with newborn/infant measures in infants of <32 weeks GA, the correlation between traditional neonatal and infant motor assessments at preterm, term, and post term ages was generally low, and the relationship between GMA and AIMS was not found. We found that infants with normal fidgety movements had better motor performance than infants with aberrant fidgety movements in the prone and supine subparameters of AIMS. In the age range of our study population fewer items can be observed in the sitting and standing subparameters as they require more advanced motor skills. Therefore, it was an expected result that there was, as yet, no difference in the sitting and standing positions between the groups. Also, due to the low number of participants the difference may not be reflected in the statistics.

A negative relationship was determined between the outcome of TINE and the AIMS total, prone, supine, sitting, and centile values. Thus, it can be seen that as the outcome of TINE deteriorated in the infants, the motor scores also decreased. However, as there were only 6 preterm infants in total showing MND in the TINE assessment and abnormal neurological syndrome, this may have prevented the determination of any relationship according to GA.

There were some limitations to this study. First, the number of infants in the GA groups was low implying that the results can not be generalized. In addition there could have been more detailed classification of the infants according to GA, such as birth at <28 weeks.

GA affects motor performance, and infants with aberrant fidgety movements have also been found to have lower motor performance. It has also been shown that abnormal neurologic findings according to TINE are negatively related to motor performance. Assessment of TINE, GMA, and AIMS together provides a detailed and complementary neuromotor assessment in preterm infants, and detecting atypical development such as MND can guide clinicians in their referalls to age-specific early intervention programs.

Declaration of Ethical Code: In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

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Effect of Smoking and Periodontitis on Adropin Level in Gingival Crevicular Fluid

Sigara ve Periodontitisin Dişeti Oluğu Sıvısındaki Adropin Düzeyine Etkisi

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ABSTRACT

Objectives: One of the most significant environmental risk factors, smoking, acts both locally and systemically to contribute to the pathophysiology and development of periodontal diseases. The purpose of this research is to quantify and contrast the levels of adropin in gingival crevicular fluid (GCF), which have a comparable mode of action to periodontal disorders and smoking-related endothelial wall dysfunction. Materials and methods: In total, 80 participants were enrolled in this study: 40 patients with chronic periodontitis (20 smokers and 20 non-smokers) and 40 healthy control patients (20 smokers and 20 non-smokers). GCF samples were obtained, and clinical parameters (plaque index, gingival index, clinical attachment level, and probing pocket depth) were noted for each participant. To measure the amount of adropin, the enzyme-linked immunosorbent assay (ELISA) method was employed. Shapiro Wilk, Mann Whitney U, Kruskall Wallis, and Chi square tests were used to statistically analyze the clinical and biochemical parameters. Results: Periodontitis, GCF adropin concentrations and periodontal clinical index averages were higher than healthy patients ($p<0.001$). There was no statistically significant difference in GCF adropin concentrations between smokers with chronic periodontitis (CPS) and nonsmokers with chronic periodontitis (CP), or between smokers who were periodontally healthy (HS) and nonsmokers who were periodontally healthy (H). Conclusions Adropin may be a potential diagnostic tool for periodontitis, regardless of smoking. However, studies investigating different biochemical parameters in GCF are needed to help understand the interaction of adropin with other mediators.

Keywords: *Periodontitis, Smoking, Gingival fluid, Adropin*

ÖZ

Amaç: En önemli çevresel risk faktörlerinden biri olan sigara, lokal ve sistemik etki göstererek periodontal hastalıkların patogenezinde ve gelişiminde rol oynamaktadır. Bu çalışmanın amacı, benzer etki mekanizmasına sahip endotel duvarında sigara içmenin ve periodontal hastalıkların neden olduğu disfonksiyonla yakından ilişkili olan diş eti oluğu sıvısındaki (DOS) adropin düzeylerini ölçmek ve karşılaştırmaktır. Gereç ve Yöntem: Bu çalışmaya 40 kronik periodontitis hastası (20 sigara içen ve 20 sigara içmeyen) ve 40 sağlıklı kontrol hastası (20 sigara içen ve 20 sigara içmeyen) olmak üzere toplam 80 kişi dahil edildi. Tüm katılımcıların klinik ölçümleri (plak indeksi, diş eti indeksi, klinik ataşman seviyesi, sondalama cep derinliği) kaydedildi ve DOS örnekleri toplandı. Adropin düzeyini analiz etmek için enzime bağlı immünosorbent tahlili (ELISA) tekniği kullanıldı. Klinik ve biyokimyasal parametrelerin istatistiksel analizi Shapiro Wilk, Mann Whitney U, Kruskall Wallis ve Ki kare testi kullanılarak yapıldı. Bulgular: Periodontitis, DOS adropin konsantrasyonları ve periodontal klinik indeks ortalamaları sağlıklı hastalara göre daha yüksekti ($p<0.001$). Kronik periodontitisli sigara içenler (CPS) ile sigara içmeyen kronik periodontitisli (CP) veya periodontal olarak sağlıklı olan sigara içenler (HS) ile periodontal olarak sağlıklı olan sigara içmeyenler (H) arasında DOS adropin konsantrasyonları açısından istatistiksel olarak anlamlı bir fark yoktu. Sonuçlar: Adropin, sigara içimine bakılmaksızın periodontitis için potansiyel bir teşhis aracı olabilir. Ancak adropinin diğer medyatörlerle etkileşiminin anlaşılmasına yardımcı olmak için DOS'daki farklı biyokimyasal parametreleri araştıran çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Periodontitis, Sigara, Dişeti oluğu sıvısı, Adropin*

INTRODUCTION

Periodontitis is an infectious disease that occurs related to relations between the pathogen microorganisms and the host in tissues that surround and support the teeth, progresses, manifests itself with progressive attachment and tooth loss, and is characterized by gingival recession and/or pocket formation (1). While bacterial plaque accumulation and host defense system have primary roles in the onset and progress of periodontal disease, the progress, severity and control of disease is affected by many local, environmental, systemic and genetic factors, and the possibility infection increases when these factors are present (2).

One of the main important environmental risk factors of periodontitis, which is defined as a 'multi-factorial' and 'eco-genetic' disease, is smoking. There is a potent correlation between smoking and the occurrence, spread and severity of periodontal diseases which has been researched for many years (3,4). According to the study conducted, it is known that an impairment occurs in the antimicrobial function, an increase is seen in the mediators playing a role in bone destruction, severity of periodontal diseases associated with the increased number of periodontopathogenic bacteria increases, and bone and attachment loss is seen in periodontal tissues, due to smoking (5). Smoking harms the immune system in a number of ways. The component in tobacco can interfere with neutrophil chemotaxis and/or phagocytosis, which alters cytokine or inflammatory mediator release. Decreased blood flow and botched revascularization in the periodontal tissues are two additional effects of smoking that postpone wound healing (6).

Cytokines and growth factors take place in inflammatory cases such as periodontal disease and tissue damage that develops due to smoking. Vascular endothelial growth factor (VEGF), one of the growth factors, has a key role in the development of periodontal disease. There are many studies suggesting that it is an important biomarker in the monitoring of the disease (7,8). Vascular endothelial growth factor also has an important role in angiogenesis and wound healing in cases of tissue damage (9). Vascular endothelial growth factor is significant in repairing endothelial damage that develops due to smoking, and in balancing the hypoxia (7). The level of VEGF has increased due to smoking and the dysfunction caused by periodontal diseases on the endothelial wall (10).

In studies performed in recent years focusing on endothelial dysfunction and maintenance of endothelial function, a new molecule has been discovered that is predicted to have an important effect on enabling vascular hemostasis. Called adropin, this molecule in peptide structure was first defined in 2008 by Kumar et al. (11). The molecular weight of adropin is about 7,927 Kda, and it is encoded over the energy homeostasis-associated gene (ENHO) that consists of 76 aminoacids. Many studies have been carried out in the field of medicine on adropin. It was shown in the first study that adropin is produced by the liver and brain tissue. Adropin is a hormone that is released mainly to participate in the insulin response and maintenance of energy balance. It regulates to fasting and nutrition (11). It has also been proven that adropin might be closely associated with glucose metabolism, dyslipidemia and metabolic syndrome (12).

The effect of adropin on the endothelium was first studied by Lovren et al. in 2010, and results were obtained proving such hypotheses (13). In a study performed using Balb/c mice in vitro and in vivo, it was observed that endothelial cells that were provided with adropin from outside showed higher proliferation, permeability of the endothelial cells decreased and they underwent TNF-alpha controlled apoptosis. Based on the results, it was concluded that adropin has a role in protecting the endothelium and enabling its sustainability (13).

In this context, adropin, a peptide hormone and a new bio-marker that takes part in the endothelial function with the activation of vascular endothelial growth factor receptor-2 (VEGFR-2) and phosphatidylinositol-3-phosphate kinase (PI3K) pathway in the vessel wall endothelium, is of great importance to present study (13). Considering that adropin might be closely associated with the

dysfunction in the endothelial wall caused by smoking and periodontal diseases, we aimed to review the adropin concentrations in the GCF samples of cases with periodontitis due to smoking.

MATERIAL and METHOD

Patient Selection and Clinical Evaluations

In total, 40 patients with chronic periodontitis (26 males/14 females, aged 28-63) 20 with smokers and 20 non-smokers, 40 individuals who were periodontally healthy (22 males/18 females, aged 20-56) 20 with smokers and 20 non-smokers participated in this study from May 2016-May 2017 at the Gaziantep University, Dentistry Faculty, Periodontology Department. In order to find a significant change of 1.4±1.5 (Effect size = 7.6-9) units in adropin levels between the chronic periodontitis smoker and periodontally healthy non-smoker groups, the minimum number of subjects required in each group was determined as 19 ($\alpha = 0.05$, $1- \beta = 0.80$) (power analysis). Inclusion criteria included the absence of any known systemic disease; have clinically healthy periodontal tissues or a diagnosis of chronic periodontitis; and the presence of ≥ 14 natural teeth in the mouth (excluding third molars). Exclusion criteria from the study; having any known systemic disease, using antibiotics and oral contraceptives in the last 6 months, having received periodontal treatment in the last 6 months, being pregnant or lactating. The study was approved by the ethics committee of the Gaziantep University of Gaziantep, Turkey (reference number 2016/128). The informed consent form was signed by all the individuals included in the study after they were informed of the aim and method of the study.
All individuals participating in our study were evaluated according to the criteria in the 1999 periodontal disease classification and categorized as periodontal healthy and chronic periodontitis (14). To evaluate the periodontal status of individuals, plaque index (PI) (15), probing depth (PD), gingival index (GI) (16) and clinical attachment level (CAL) were measured and a periodontal examination including radiographic evaluation was performed. Williams periodontal probe (Hu-Friedy, Chicago, Illinois, USA) was used to measure clinical periodontal parameters. Measurement of clinical periodontal parameters and collection of GCF samples were performed by a single trained investigator (B.O.). Periodontally healthy individuals had no probing depth (PD) (PD≤3 mm) and no radiographic bone loss. Twenty smokers and 20 non-smokers with chronic periodontitis diagnosis established in clinic and radiologic examination, a clinic attachment loss (CAL) mouth mean value ≥ 4 mm, and a PD ≥ 5 mm in at least 20 areas were included in the study. Patients who have smoked at least 10 cigarettes a day for at least five years were examined in the smoker group, whereas patients who never smoked in their lives or quit smoking two years ago were examined in the non-smoker group. Smoking status was determined by asking individuals. Package year was obtained by dividing the number of cigarettes smoked a day by 20, and multiplying the result with the number of smoker years (17).

Collection and Quantification of GCF Samples

On the day following the clinical assessments (24 hours later), GCF samples were taken from a total of 4 teeth per session in the area with highest pocket depth during probing in each quadrant of the patients using sterilized paper strips (Periopaper® , OraFlow Inc., PlainView, New York, USA). Then each paper strip was placed inside the gingival pocket until a slight resistance was felt, and left there for 30 seconds (18). Samples with blood and saliva were not included in the evaluation. Gingival crevicular fluid volume of the strips were measured and recorded in the pre-calibrated Periotron 8000 device (Orafow Inc., Plainview, New York, USA). Paper strips including the GCF samples were put in an Eppendorf tube and stored at -80 degrees until day of analysis.

Biochemical Analysis of Adropin

For the analysis, 500 µL serum physiologic was added to the GCF samples in the Eppendorf tube, and samples were left at +4°C for one night. Once the waiting period was over, Eppendorf tubes were centrifuged, supernatant was separated, and adropin measurement was made in the supernatant. Adropin (Phoenix, ABD) level was measured using the ELISA method in the samples.

This kit measures the adropin level using the quantitative competition sandwich enzyme immunoassay technique in 5 hours. Color intensity was measured at 450 nm using the ELISA reader (Biotek Instruments, ABD) spectrophotometrically and adropin levels were calculated using standard graphics.

Statistical Analysis

The Shapiro-Wilk test was used in the statistical analysis of the data to check the normal distribution of numerical information. In order to cross-check variables that did not have a normal distribution in two groups, the Mann Whitney U Test was utilized. When comparing numerical data with a normal distribution between four groups, ANOVA and LSD multiple comparison tests were employed, whereas Kruskal Wallis and Allpairwise tests were used when comparing data with a non-normal distribution between four groups. The Spearman Rank correlation coefficient and the Chi-Square test were used to examine the correlation between numerical variables and categorical variables, respectively. For both descriptive statistics and categorical variables, the mean value was expressed as ±standard deviation and in percentage terms, respectively. Software from the SPSS 22.0 package was used for the analysis. Statistical significance was defined as $P<0.05$.

RESULTS

Present study consisted of 80 patients divided into 4 groups as smokers with chronic periodontitis (CPS) (4 females, 16 males), non-smokers with chronic periodontitis (CP) (10 females, 10 males), smokers with periodontally healthy (HS) (5 females, 15 males) and non-smokers with periodontally healthy (H) (13 females, 7 males). The mean age ± standard deviation value of participants was 37.51±11.21. Intergroup changes and comparisons related to the clinical and laboratory findings including sample area clinical data (PI, GI, SCD, CAL), whole mouth clinical data (PI(t), GI(t), SCD(t), CAL(t)), GCF volume measurements and GCF adropin concentrations have been given in Table 1.

According to the result of the statistical evaluation performed, whole mouth (PI(t), PD(t), GI(t), CAL(t)), sample area (PI, PD, GI, CAL) clinical data and GCF volume (µl) value were higher at a statistically significant level in the group with chronic periodontitis (CPS and CP) as compared to the healthy group (HS and H) ($p<0.001$). No statistically significant difference was seen between CPS and CP, and the HS and H (Figure 1).

According to the GCF adropin concentrations, adropin values of the group with chronic periodontitis (CPS and CP) were observed to be higher at a statistically significant level as compared to the healthy group (H) ($p<0.001$). Adropin values of the group with chronic periodontitis (CPS and CP) were found to be higher at a statistically significant level as compared to HS group ($p<0.05$) (Figure 2). Even though GCF adropin concentration was observed to be higher in CPS as compared to CP as well as HS as compared to H, no statistically significant difference was seen. Only a positive association was observed in the CPS group between GCF adropin levels and PD values; there was no link identified between gingival inflammatory indicators and GCF adropin levels.

Table.1 Clinical Periodontal Parameters of All Groups

	CPS (N=20) **α**	**CP** (N=20) **β**	**HS** (N=20) **γ**	**H** (N=20) **δ**	P
PI(t) †	2.56±0.51	2.48±0.48	0.09±0.14	0.03±0.06	** αγ, αδ, βγ, βδ
PD(t) (mm) †	4.89±0.50	4.67±0.43	1.55±0.27	1.60±0.20	** αγ, αδ, βγ, βδ
GI(t) †	2.05±0.26	2.04±0.13	0.04±0.06	0.07±0.07	** αγ, αδ, βγ, βδ
CAL(t) (mm) †	5.05±0.58	4.74±0.43	1.55±0.27	1.60±0.20	** αγ, αδ, βγ, βδ
PI †	2.52±0.45	2.49±0.48	0.13±0.19	0.04±0.12	** αγ, αδ, βγ, βδ
PD (mm) †	7.68±1.25	7.65±1.11	1.63±0.33	1.68±0.30	** αγ, αδ, βγ, βδ
GI †	2.03±0.26	2.06±0.20	0.06±0.11	0.16±0.19	** αγ, αδ, βγ, βδ
CAL (mm) †	8.00±1,206	7.76±1.15	1.63±0.33	1.68±0.30	** αγ, αδ, βγ, βδ
GCF Volume (µl) †	0.88±0.20	0.91±0.19	0.07±0.07	0.11±0.09	** αγ, αδ, βγ, βδ
Adr (ng/mL) †	0.54±0.39	0.47±0.25	0.30±0.14	0.25±0.12	** αδ, βδ * αγ, βγ

CPS(α): Smokers with chronic periodontitis, **CP(β):** Non-smokers with chroni periodontitis, **HS(γ):** Smokers with periodontally healthy, **H(δ):** Non-smokers with periodontally healthy
PI(t): Plaque index total, **PD(t):** Probing depth, **GI(t):** Gingival index total, **CAL(t):** Clinical attachment level total, **PI:** Plaque index sample area, **PD:** Probing depth sample area, **GI:** Gingival index sample area, **CAL:** Clinical attachment level sample area

† mean ± std. deviation

* Statistically significant ($p<0.05$)

**Statistically highly significant ($p<0.001$)

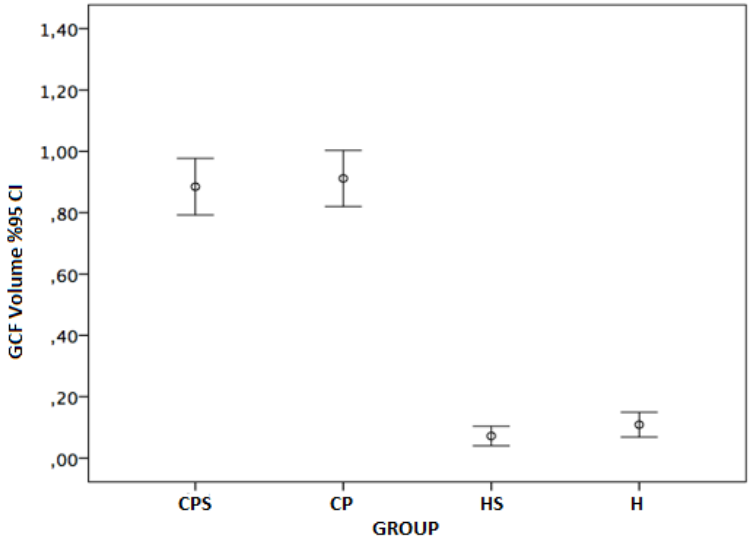

Figure 1: Gingival crevicular fluid volume (µl) values of groups

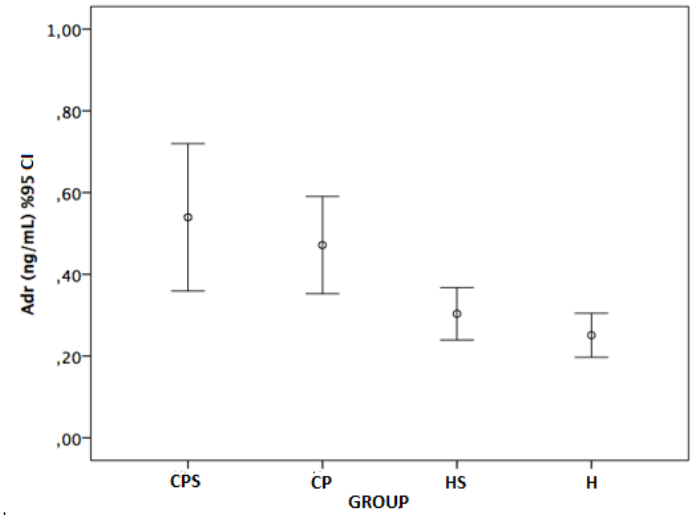

Figure 2: Gingival crevicular fluid adropin concentrations (ng/mL) of groups

DISCUSSION

In terms of determining GCF adropin concentrations in healthy and periodontitis areas, the degree of cigarette smoking influencing these concentrations, and the relationships between GCF adropin concentrations and clinical parameters, this study is the first that we are aware of. Present study is a new study that examines the extent to which smoking affects the adropin level, one of the peptide hormones, in healthy individuals and those with periodontitis.

Smoking is considered one of the most important factors in the onset and advancement of destructive periodontal diseases. Action mechanism of smoking on the oral health has not been understood completely. According to the literature review, there are many studies examining the effect of smoking on periodontal clinical parameters, and these studies suggest inconsistent results (3,4).

In some studies, PI increases with smoking, which makes the researchers believe that the oral health of smokers is worse than that of non-smokers (19,20). In a study carried out by Feldman et al., less plaque accumulation was reported in smokers (21). Other studies show that smoking has no apparent effect on the PI (22,23). Present study supports this information. Even though the PI values of the smoker individuals in periodontitis and healthy groups are higher than those of the non-smokers, the difference between them is not statistically significant.

Although there are many studies showing the GI increases with smoking (22,24), GI decreases with smoking in some studies (25,26). There are many studies in literature showing that smoking has no apparent effect on GI (27,28). While mean GI values of the individuals in healthy group are near-zero, it is seen to cause an insignificant decrease depending on the smoking status. This shows that smoking suppresses the gingivitis that occurs as a response to the available dental plaque, and several studies performed support this information (23,29).

While it is emphasized in some studies that periodontal bone loss is seen in smoker individuals with good oral hygiene (28) and PD increased with smoking (21,31,32); in our study, even though the clinical attachment loss and PD values of the smoker individuals in periodontitis and healthy groups are higher than those of the non-smokers, the difference between them is not statistically significant. We think that no significant difference occurred in present study based on the smoking state, since the selection criteria were limited (CALmean≥4) (PDmean≥5 mm). This result might be associated with the absence of an apparent difference between the oral hygiene of smoker and non-smoker patients included in the study.

Smoking affected the GCF volume in a negative way, which is associated with the reduction in the early findings of inflammation along with the vasoconstriction that occurs in vessels with smoking (33,34). Present study supports this information, and even though the GCF volume of the smoker individuals in periodontitis and healthy groups are lower than those of the non-smokers, the difference between them is not statistically significant.

In present study, adropin was determined in all of the GCF samples. According to the literature review, our study is the first that evaluated adropin concentration in GCF around natural teeth. In studies on systemic diseases, adropin was found in various body fluids. Many samples such as serum, plasma, tissue samples and cell cultures were used (35-37). It is understood with this study that although the GCF adropin concentrations are lower than the adropin concentrations in other body fluids, gingival crevicular fluid can be used in the examination of the effect of adropin on periodontal tissues.

In literature, there are many studies examining the periodontal disease-hormone relationship (38,39). Thanks to studies performed in recent years, it was concluded that peptide hormones are produced in periodontal cells, and contribute to periodontal infection and recovery (40). The body uses peptide hormones such as adiponectin, leptin, and adropin for similar purposes. Recent research has shown

that leptin and adiponectin, which are well-known for their impacts on metabolism, reproduction, and body weight management, can directly affect immunological responses and may have a role in certain inflammatory illnesses, including periodontitis (40, 41).

As a result of the literature review we have performed, many studies have been found examining the relationship of leptin-periodontitis and adiponectin-periodontitis. While other authors have shown no changes in plasma leptin levels throughout the inflammation, some investigations have revealed elevated levels of the protein consistent with chronic inflammation (42,43, 44, 45). It has been proposed that endothelial dysfunction during chronic inflammation causes an increase in leptin levels (46).

To our knowledge, there is no study that examines the relationship of adropin-periodontitis. The molecular weight of adropin in peptide structure is about 7,927 Kda, and it is encoded over the ENHO that consists of 76 aminoacids (11). Having a protective and regulating role in the endothelial function, adropin molecule regulates VEGFR-2 pathway in the endothelium, enables continuity of the operation of endothelial function, and acts to prevent endothelium dysfunction (13). Smoking and periodontal disease have resulted in endothelial dysfunction on the endothelial wall, therefore the level of VEGF has increased (10). In a study that investigated the VEGF level of patients with periodontitis, gingival crevicular fluid VEGF amount collected from the diseased areas in patients with periodontitis was found to be higher than those collected from the clinically healthy areas (47). In another study performed, VEGF levels of healthy, gingivitis, periodontitis and post-periodontal treatment groups were compared (9). The VEGF level was found to be higher at a statistically significant level in the periodontitis group as compared to the control group, and a decrease was observed in the post-treatment VEGF level (9). In a study evaluating the VEGF levels in periodontal tissue and GCF in health and disease groups, VEGF level in the periodontitis group was observed to be significantly higher as compared to the healthy group. The reason behind such an increase was associated with the role played by PGE_2, 1L-1 and TNF-a in GCF which emerge in case of periodontal disease, in the induction of VEGF (48). In a study performed by Johnson et al., VEGF and IL-6 levels were investigated in patients that were healthy (≤3mm), had gingivitis (≤3mm) and had a periodontal pocket of 4-6mm and >6mm, and VEGF and IL-6 level in healthy patients were found to be lower in patients with periodontitis (47). VEGF concentration was higher in patients with a periodontal pocket of 4-6 mm as compared to those with >6mm. The reason behind this is believed to be the fact that VEGF increases since the vascularization increases at the onset and progress phase during the shift from gingivitis to periodontitis (47).

Gundogar et al. examined the adropin level in the peri-implant sulcus in peri-implant patients. In this study, PISF adropin levels, a statistically significant difference was noted between PI and H groups ($p>0.05$), ($p<0.05$) (47).

According to our study, adropin concentrations of the group with chronic periodontitis (CPS and CP) were observed to be higher at a statistically significant level as compared to the H ($p<0.001$) and HS ($p<0.05$). All of these studies support our study. In particular, the increase in adropin in the PI group in the study of Gundogar et al. is consistent with the increase in adropin concentration in the periodontitis group in our study (49).

On the other hand, a study that examines the effect of smoking have shown that the plasma leptin levels are lower in smokers (50). However, others have suggested higher plasma leptin levels in smokers and long-term nicotine gum users than in non-smokers (51,52). There are inconsistent results in this subject. The effect of smoking on VEGF level was researched in the study performed by Booth et al. (48), and it was seen that smokers had lower saliva VEGF levels as compared to non-smokers in the one-way analysis of variance. However, VEGF levels were not affected by smoking in the 2-way analysis of variance. In another study, an increase was seen in mediators such as vasoproliferative agents and VEGF depending on exposure to smoking (53).

Depending on these studies, it was concluded that smoking blocked the eNOS/NOS pathway irreversibly, and led to an over-accumulation in the VEGF/VEGFR2 that activates this pathway which was blocked in an irreversible way. According to our study, GCF adropin concentration was observed to be higher in CPS as compared to CP as well as HS as compared to H, no statistically significant difference was seen. Our study also supports this information, and the increase in adropin concentration of patients with periodontitis is believed to be related to the increase in VEGF, which has a pro-inflammatory effect in inflammatory diseases such as periodontitis. The absence of smoking's effect on adropin concentration is attributed to the fact that no statistically significant difference was seen in the GCF adropin concentration since smoking blocks the eNOS/NOS pathway irreversibly and leads to accumulation in the VEGF/VEGFR2. However, it is still not known at which step of this pathway smoking blocks it using which action mechanisms. Multicenter studies may be needed to understand this situation.

Furthermore, the study by Bozkurt et al. indicated that only a positive association was observed between GCF leptin concentrations and PD values from 4 to 5 mm in the smokers group, and no link was identified between the GCF leptin concentrations and gingival inflammatory measures (54). Similar to this study, ours also observed no link between gingival inflammatory parameters and GCF adropin concentrations, but only a positive correlation between GCF adropin concentrations and PD values in the CPS group. As a result, smoking may not directly affect peptid hormones. Studies with larger participation are needed to fully understand the relationship between adropin and smoking.

CONCLUSION

The aim of present study was to review the adropin concentration in the GCF of patients with periodontitis, considering that adropin might be closely associated with the dysfunction caused by smoking and periodontal diseases in the endothelial wall. Based on the results of this study, we believe that GCF adropin concentrations in periodontal disease and health cases is affected by the periodontal inflammatory state rather than smoking. Since adropin is a new mediator, there is a need for multi-center studies with a larger participation in order to fully understand the relationship between adropin, which is a peptide hormone and related to many systemic diseases, and the periodontal tissues. We believe that adropin will be subject to more studies in the literature in the future, and an important marker in the diagnosis and treatment of periodontal diseases.

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Declaration of Ethical Code: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration and its later amendments. Individuals without systemic disease were included in this study from May 2016-May 2017 at the Gaziantep University, Dentistry Faculty, Periodontology Department. The study was approved by the ethics committee of the Gaziantep University of Gaziantep, Turkey (amended protocol 2016/128 and an approval was obtained dated 05.02.2016).
In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

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Kalıtsal Trombofili ve COVID-19 İlişkisinin Retrospektif Olarak Araştırılması: Tek Merkez Deneyimi

Retrospective Investigation of the Relationship between Hereditary Thrombophilia and COVID-19: A Single Center Experience

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ÖZ

Amaç: COVID-19, SARS-CoV-2'un neden olduğu, tüm sistemleri etkileyen ve en önemli etkisini trombofili yoluyla göstermekte olan yıkıcı bir pandemi durumudur. Bu çalışmada kalıtsal trombofili yatkınlığı genleri incelenen hastalarda genotip ile COVID-19 fenotipi arasındaki ilişkinin araştırılması amaçlanmıştır. Gereç ve Yöntemler: Çalışmanın örneklemi, 2017-2021 yılları arasında, Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Tıbbi Genetik Bölümü'nde kalıtsal trombofili yatkınlık genleri analiz edilmiş olan hastalardan seçilmiştir. Genetik analizi gerçekleşmiş ve COVID-19 teşhis edilen 66 hastanın genotip-fenotip ilişkisi araştırılmıştır. Bulgular: Hastalardan 2'sinde heterozigot *protrombin (FII)-G20210A*, 11'inde heterozigot *Faktör V Leiden (FVL)-G1691A*, 15'inde *plazminojen aktivatör inhibitörü-1 (PAI) 4G/4G*, 30'unda *PAI 4G/5G*, 2'sinde homozigot *F13*, 15'inde heterozigot *F13*, 23'ünde heterozigot *Metilen tetrahidrofolat redüktaz (MTHFR) C677T* (bunların 10'u birleşik heterozigot), 10'u homozigot *MTHFR C677T*, 24'ünde heterozigot *MTHFR A1298C* (bunların 10'u birleşik heterozigot), 10'u homozigot *MTHFR A1298C* genomik değişimleri saptanmıştır. *FVL* heterozigotluk durumu ile tanı anında takipne ve hipotansiyon arasında anlamlı bir ilişki saptanmıştır. Aktif sigara içen veya geçmişte sigara içmiş olan vakaların hiç sigara içmeyenlere kıyasla önemli lenfopenisi olduğu görülmüştür. Ayrıca aktif sigara kullanıcılarında, sigara kullanmayanlara göre troponin düzeyleri de daha yüksek olarak saptanmıştır. Sonuç: COVID-19 olgularında, kalıtsal trombofili genlerinin araştırılması farklı klinik bulguların açıklanmasında yardımcı olabilir. Bu çalışmadan elde edilen veriler, COVID-19 tanısı alan hastalarda, hastalığın klinik bulgularının, *FVL* heterozigotluk durumu ve sigara kullanımından önemli ölçüde etkilendiğini göstermiştir.

Anahtar Kelimeler: *COVID-19, SARS-Cov-2, Kalıtsal trombofili, Genetik test, Sigara kullanımı*

ABSTRACT

Objective: COVID-19 is a devastating pandemic caused by SARS-CoV-2, affecting all systems and showing its most important effect through thrombophilia. This study aimed to investigate the relationship between genotype and COVID-19 phenotype in patients whose hereditary thrombophilia susceptibility genes were examined. Material and Methods: The sample of the study was selected from patients whose hereditary thrombophilia susceptibility genes were analyzed at the Medical Genetics Department of Dışkapı Yıldırım Beyazıt Training and Research Hospital, between 2017 and 2021. The genotype-phenotype relationship was investigated in 66 patients whose genetic analysis was performed and diagnosed with COVID-19. Results: Heterozygous *prothrombin (FII)-G20210A* in 2 patients, heterozygous *Factor V Leiden (FVL)-G1691A* in 11 patients, *plasminogen activator inhibitor-1 (PAI) 4G/4G* in 15 patients, *PAI 4G/5G* in 30 patients, 2 were homozygous *F13*, 15 were heterozygous *F13*, 23 were heterozygous *Methylene tetrahydrofolate reductase (MTHFR) C677T* (10 of them compound heterozygous), 10 were homozygous *MTHFR C677T*, 24 were heterozygous *MTHFR A1298C* (10 of them combined heterozygous), 10 of which were homozygous *MTHFR A1298C* genomic alterations were detected. A significant relationship was detected between *FVL* heterozygosity status and tachypnea and hypotension at diagnosis. Cases who were active smokers or had smoked in the past had significant lymphopenia compared to never-smokers. Additionally, troponin levels were found to be higher in active smokers compared to non-smokers. Conclusion: In COVID-19 cases, investigating hereditary thrombophilia genes may help explain clinical findings. Data from this study have shown that in patients diagnosed with COVID-19, the clinical presentation of the disease is significantly affected by the state of *FVL* heterozygosity and smoking.

Keywords: *COVID-19, SARS-CoV-2, Hereditary thrombophilia, Genetic testing, smoking*

GİRİŞ

İlk olarak Aralık 2019'da Wuhan'da gözlenen COVID-19, şiddetli akut solunum sendromu koronavirüs 2'nin (SARS-CoV-2) yol açtığı pandemiye neden olmuş bir hastalıktır (1). Bu virüsle enfekte hastalarda; asemptomatik hastalık, hafif üst solunum yolu enfeksiyonu, ölümle sonuçlanabilecek solunum yetmezliği ve çoklu organ yetmezliği gibi geniş spektrumda klinik bulgular gözlenebilmektedir. COVID-19 hastalarında tipik olarak görülen ve sık rastlanan semptomlar ateş, öksürük ve nefes darlığı iken daha az görülen semptomlar burun akıntısı, boğaz ağrısı, miyalji/yorgunluk, baş ağrısı ve ishal olarak bildirilmiştir (1,2). Yaygın laboratuvar bulguları arasında lenfopeni ve CRP yüksekliği bulunurken, özellikle koagülopati ile komplike olan vakalarda yüksek D-dimer, trombositopeni, uzamış PT, yüksek fibrinojen, yüksek laktat dehidrogenaz ve yüksek ferritin bulunur (3-8). Yüksek risk altındaki semptomatik bireylerde gözlenen en yaygın akciğer BT anormallikleri; sıklıkla iki taraflı ve periferik dağılıma sahip olup, alt lobları içermektedir. Literatürde; göğüs BT ile COVID-19 ilişkisinin araştırıldığı ve 13 bağımsız çalışmanın dahil edildiği geniş çaplı bir meta-analizin sonuçlarına göre, hastalarda buzlu cam opaklaşması yaklaşık %83, karışık konsolidasyonla birlikte buzlu cam opaklaşması ise yaklaşık %58 olarak bildirilmiş olup, interlobüler septal kalınlaşma, komşu plevra kalınlaşması ve hava bronkogramı insidansları da yüksek olarak tespit edilmiştir (9). COVID-19 hastalığı, aşırı inflamatuar yanıt, düzensiz hemostaz ve yüksek trombotik risk ile ilişkilidir (6,7). Tüm sistemleri etkileyebilen COVID-19, en önemli etkisini trombofili yoluyla göstermektedir. Trombofili, tromboz (kan damarlarında trombüs oluşumu) riskini artıran bir pıhtılaşma anormalliğidir ve genellikle pıhtılaşma kademesinde veya antikoagülasyon/fibrinolitik sistemde meydana gelen dengesizliği yansıtır (10,11). Trombofili kalıtsal ve edinsel olarak görülebilir. Kalıtsal trombofili, doğal antikoagülanların (antitrombin, protein C ve protein S) eksikliği, homosistein değerlerinin artması ve fibrinojen ve pıhtılaşma faktörlerindeki değişikliklerden kaynaklanmaktadır. Edinsel trombofili ise, otoimmün bozukluklar (antifosfolipid sendromu), travma veya malignite gibi ikincil hastalıkların bir sonucu olarak ortaya çıkabilir. Trombofiliye neden olan faktörler, çoğunlukla hem kalıtsal hem de edinsel nedenlerin bir arada bulunması şeklinde görülür ve klinik tablonun ağırlaşmasına neden olmaktadır. Kalıtsal trombofilinin başlıca nedenleri; *protrombin (FII)-G20210A* ve *Faktör V Leiden-G1691A* olarak bildirilmiştir (12). Literatür araştırmasında, COVID-19 hastalarında trombofili ile hastalık şiddeti arasında ilişki olduğunu gösteren çalışmalar mevcuttur (12-15). Bu çalışmada, trombofiliye yatkınlık oluşturan genler ile COVID-19 hastalığının klinik bulguları arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

GEREÇ ve YÖNTEM

Bu retrospektif çalışma Dünya Tabipler Birliği ve Helsinki Bildirgesi'nde bildirilen etik sorumluluklar dikkate alınarak gerçekleştirilmiş olup Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi'nin, Girişimsel Olmayan Klinik Araştırma Etik Kurulu tarafından onaylanmıştır (Belge No: 2021-112/12). Çalışmaya, daha önce kalıtsal trombofili yatkınlık genleri analiz edilmiş ve COVID-19 tanısı almış 66 hasta dahil edildi. Araştırma ile ilgili bilgilendirilen ve bilgilerinin kullanılmasına izin veren hastalara ait klinik bilgiler, muayene ve izlem dosyalarından elde edilmiştir. Daha önceden gerçekleşmiş olan moleküler çalışmada, hastalardan 2 ml periferik venöz kan örnekleri Etilen Diamin Tetra Asetikasit'li (EDTA) tüplere alınmış ve genomik materyalin izole edilmesinde, otomatik DNA izolasyon sistemi olan QIAcube® (Qiagen Inc. Mississauga, Kanada) kullanılmıştır. Bir spektrofotometrik ölçüm cihazı olan ND-1000 (Nano-Drop Technologies, Wilmington, DE, ABD) ile, elde edilen DNA'nın konsantrasyon ve kalitesinin değerlendirilmesi sağlanmış olup, uygun saflık/konsantrasyonu (OD260/OD280, 1.8-2.0) olan genomik materyaller çalışmaya dahil edilmiştir. Elde edilen DNA materyaline herediter trombofili yatkınlık gen bölgelerine spesifik olan primer problar (çalışılacak bölgeye özel dizayn edilen küçük DNA parçaları) kullanılmıştır. Araştırılan gen bölgeleri; *Faktör V Leiden-G1691A (FVL), Faktör II-G20210A, MTHFR-C677T, MTHFR-A1298C, PAI-1–4G/5G, Faktör XIII-V34L* olarak sıralanmıştır. "Thrombophilia Multiplex Real Time PCR Kit" kullanılarak Real-Time PCR tekniği ile yapılan genetik analiz, "Rotor-Gene Q" cihazında gerçekleştirilmiştir.

Bu çalışmada, moleküler analiz gerçekleştirilmiş olan hastalardaki, herediter trombofili yatkınlık gen bölgeleri değişimleri ile hastaların demografik bulguları (cinsiyet, yaş, kronik hastalık, sigara içimi), COVID-19 tanısı konulan hastaların başvuru sırasındaki klinik (ateş, öksürük, solunum sıkıntısı, halsizlik, yorgunluk, myalji, gastro intestinal semptomlar, anosmi, takipne, taşikardi, hipotansiyon) ve laboratuvar bulguları(hipoksemi, lökosit, lenfosit, trombosit, hemoglobin, ALT/AST, üre, kreatinin, albümin, Ca, total bilirubin, LDH, CRP, Prokalsitonin, troponin, ferritin, D-Dimer, fibrinojen ve laktat düzeyleri) arasındaki ilişki incelenmiştir.

İstatiksel Analiz

Elde edilen veriler, SPSS 25.0 (IBM Inc, Chicago, IL, USA) versiyon programına girilerek analiz edildi. Tanımlayıcı istatistiklerde kalitatif veriler, oranlar ve ortanca değer ile; kantitatif veriler ortalama ± standart sapma (SS) ile ifade edildi. Dağılımları arasındaki farklılıklar Ki-kare analizi ile incelenmiştir. Tüm analizlerde $p<0,05$ değeri istatistiksel olarak anlamlı sonuç olarak kabul edildi.

BULGULAR

Çalışmaya katılanların 44'ü (%66,7) kadın, 22'si (%33,3) erkek cinsiyette olup, yaş ortalaması 41,74 olarak tespit edilmiştir. Olguların 26'sında (%39,4) tanı konulmuş bir hastalık yokken, kalan 40 (%60,6) olguda komorbidite (hipertansiyon, KOAH, geçirilmiş pulmoner tromboemboli öyküsü, kardiyovasküler hastalık gibi) rapor edildi (Tablo 1).

Tablo 1: Hastaların Tanı Anında Klinik ve Laboratuvar Bulgularının Dağılımı

Klinik Bulgular		Hasta sayısı (n)	Hasta oranı (%)
Komorbidite (hipertansiyon, KOAH, geçirilmiş pulmoner tromboemboli öyküsü, kardiyovasküler hastalık)	Var	40	60,6
	Yok	26	39,4
Sigara kullanım öyküsü	Hiç kullanmamış	42	63,6
	Sigarayı bırakmış	10	15,2
	Aktif kullanıcı	14	21,2
Yüksek Ateş		27	40,9
Öksürük		31	47
Solunum sıkıntısı		18	27,3
Halsizlik		60	90,9
Myalji		65	98,5
Anosmi		15	22,7
GIS semptomları		20	30,3
Takipne		15	22,7
Hipotansiyon		7	10,6
Taşikardi		3	4,5
Hipoksemi		4	6,1
Sedimentasyon yüksekliği		66	100
Lökosit sayısı	Normal	35	53
	Düşük	2	3
	Yüksek	29	43,9
Fibrinojen	Normal	50	75,8
	Düşük	10	15,2
	Yüksek	6	9,1
Prokalsitonin	Normal	4	6,1
	Düşük risk	16	24,2
	Orta risk	46	69,7
Nötropeni	Yok	64	97
	Var	2	3
Lenfopeni	Yok	26	39,4
	Var	40	60,6
Trombosit sayısı	Normal	66	100

Hemoglobin	Normal	51	77,3
	Düşük	15	22,7
ALT	Normal	48	72,7
	Yüksek	18	27,3
AST	Normal	50	75,8
	Yüksek	16	24,2
Üre	Normal	51	77,3
	Yüksek	15	22,7
Kreatinin	Normal	34	51,5
	Yüksek	32	48,5
Albümin	Normal	40	60,6
	Yüksek	26	39,4
Total Bilirubin	Normal	65	98,5
	Yüksek	1	1,5
LDH	Normal	47	71,2
	Yüksek	19	28,8
CRP	Normal	13	19,7
	Yüksek	53	80,3
Troponin	Normal	60	90,9
	Yüksek	6	9,1
PO2	Normal	46	69,7
	Yüksek	20	30,3
CK-MB	Normal	62	93,9
	Yüksek	4	6,1
Ferritin	Normal	62	93,9
	Yüksek	4	6,1
D-Dimer	Normal	46	69,7
	Yüksek	20	30,3
Laktat	Normal	54	81,8
	Yüksek	12	18,2
Pnömoni	Var	40	60,6
	Yok	26	39,4

Bu komorbiditeler, kadın hastaların 24'ünde (%54,5) ve erkek hastaların 16'sında (%72,7) tespit edildi. Yapılan istatistiksel analiz (Ki-Kare Test) sonucunda, zigosite durumuna bakılmaksızın trombofili ilişkili genotip ile komorbidite arasında anlamlı bir fark bulunamamıştır (Tablo 2).

Tablo 2: Komorbidite ve Trombofili İlişkili Genlerin İlişkilerinin Analiz Sonuçları

Genotip	Zigosite	Komorbidite (Var)	Komorbidite (Yok)	*P* değeri
	Heterozigot	1	1	*0,097*
Faktör II-G20210A	Homozigot	0	0	
	Normal	39	25	
	Heterozigot	8	3	*0,812*
Faktör V Leiden-G1691A	Homozigot	0	0	
	Normal	32	23	
	Heterozigot	20	10	*1,697*
PAI-1	Homozigot	7	8	
	Normal	13	8	
	Heterozigot	10	5	*1,777*
Faktör XIII-V34L	Homozigot	2	0	
	Normal	28	21	
	Heterozigot	15	8	*0,333*
MTHFRC677T	Homozigot	6	4	
	Normal	19	14	
	Heterozigot	13	11	*1,777*
MTHFRA1298C	Homozigot	5	5	
	Normal	22	10	

Çalışmaya dahil edilen hastaların moleküler genetik analiz sonuçları Tablo 3'de özetlenmiştir.

Tablo 3: Hastaların Moleküler Genetik Analiz Sonuçları

Genotip	Zigosite	Hasta sayısı (n)	Hasta oranı (%)
Faktör II-G20210A	Heterozigot	2	3
Faktör V Leiden-G1691A	Heterozigot	11	16,7
PAI-1–4G/4G	Homozigot	15	22,7
PAI-1–4G/5G	Heterozigot	30	45,5
PAI-1–5G/5G	Homozigot	21	31,8
Faktör XIII-V34L	Homozigot	2	3
Faktör XIII-V34L	Heterozigot	15	22,7
MTHFRC677T	Heterozigot	23 (10'u birleşik heterozigot olgu)	34,8
MTHFRC677T	Homozigot	10	15,2
MTHFRA1298C	Heterozigot	24 (10'u birleşik heterozigot olgu)	36,4
MTHFRA1298C	Homozigot	10	15,2

FVL heterozigot hastalar ve normal genotipte olanlar istatistiksel olarak karşılaştırıldığında, yüksek ateş, öksürük, solunum sıkıntısı, halsizlik, myalji, GİS semptomları, anosmi, taşikardi, hipoksemi, tanı anı lökosit, hemoglobin, ALT, AST, üre, kreatinin, albümin, total bilirubin, LDH, CRP, troponin, prokalsitonin, CK-MB, D-Dimer, fibrinojen, laktat, PO2 düzeyleri, pnömoni gelişimi, nötropeni ve lenfopeni varlığı açısından anlamlı bir farklılık bulunamadı.

FVL normal genotipte olan 55 hastadan yalnızca 10'unda (%18,2) tanı anında takipne varken, *FVL* heterozigot durumdaki 11 hastadan 5'inde (%45,5) tanı anında takipne vardı. *FVL* normal genotipte olan 55 hastanın 4'ünde (%7,3) tanı anında hipotansiyon teşhis edildi ve *FVL* heterozigot olan 11 hastanın 3'ünde (%27,3) tanı anında hipotansiyon gözlendi. *FVL* heterozigotluk durumu ile hem tanı anında takipne hem de tanı anında hipotansiyon arasında anlamlı bir ilişki saptandı (p=0,049).

Normal genotipte olan hastalar ve *Faktör XIII-V34L, PAI 4G/5G* ve *MTHFR 677/1298* heterozigot/homozigot hastalar arasında bu sayılan parametrelerin tamamında anlamlı bir farklılık bulunamadı. Bu çalışmada yalnızca 2 hastada heterozigot *Faktör II-G20210A* genotipi saptandığı için istatistiksel bir analiz gerçekleştirilebilmesi mümkün olmadı.

Çalışmaya katılan olguların 42'si (%63,6) yaşamları boyunca hiç sigara içmemişti ve 14'ü (%21,2) 10 yıl ve daha uzun zamandır sigara kullananlardı. Kalan 10 (%15,2) olgu ise 5 yıl ve daha uzun zamandır sigarayı bırakmış olan hastalardı (Tablo 1). Sigarayı halen içiyor olan ve geçmişte içmiş olan hastalarda, sigara hiç içmemiş olanlarla kıyaslandığında, anlamlı düzeyde lenfopeni tespit edildi (p=0,02). Sigara içmek ve tanı anı troponin yüksekliği arasında da anlamlı bir ilişki vardı (p=0,015). Halen sigara içen hastaların, sigarayı hiç içmemiş vaya geçmişte bırakmış olanlara göre troponin düzeyleri daha yüksek bulundu (p=0,004).

Sigara değişkeni ile yüksek ateş, öksürük, solunum sıkıntısı, halsizlik, myalji, GIS semptomları, anosmi, takipne, hipotansiyon, taşikardi, hipoksemi, lökosit düzeyleri, trombosit düzeyleri, nötropeni varlığı, hemoglobin düzeyleri, ALT, AST, üre, kreatinin, albümin, total bilirubin, LDH, CRP, prokalsitonin, CK-MB, D-Dimer, fibrinojen, laktat, PO2 düzeyleri, pnömoni gelişimi, nötropeni ve lenfopeni parametreleri arasında anlamlı bir ilişki gözlenmedi.

TARTIŞMA ve SONUÇ

Literatürdeki çok sayıda çalışmada, trombozun COVID-19 hastalarında meydana gelebilecek en ciddi komplikasyonlardan biri olduğu ve bu hastalarda trombotik komplikasyon görülme sıklığının %80 oranına yaklaştığı raporlanmıştır (16,17).

Özellikle yoğun bakım ünitesinde tedavi görmüş olan COVID-19 hastalarında, hiperkoagülasyon durumunun varlığını araştıran çok sayıda araştırma, olguların tromboz insidanslarının %30-80 arasında değiştiğini bildirmiştir. COVID-19 tanısı konulmuş ve yoğun bakımda izlenen bu hastalarda mikrovasküler emboli ve pıhtılaşma bozuklukları nedeniyle klinik tablonun kötüleştiği, koagülopati gelişenlerde ise mortalitenin daha yüksek sıklıkta gözlendiği rapor edilmiştir (17-20).

COVID-19 tanılı fakat yoğun bakım ihtiyacı olmayan hastalarda tromboz insidanslarının %9-15 arasında olduğu gösterilmiştir. Yoğun bakım ünitesinde tedavi alan hastalarda tromboz riskinin daha yüksek görülmesinin nedeni, enfeksiyonun daha şiddetli olması nedeniyle bu hastalarda görülen pro-inflamatuar ve anti-fibrinolitik durumun artması olabileceği düşünülmüştür (20,21).

Literatürde bildirilen çok merkezli bir çalışmada, COVID-19 enfeksiyonu nedeniyle ölen 54 hastada, şiddetli lenfopeninin yanı sıra D-dimer, kardiyak troponin, ferritin, laktat dehidrogenaz ve IL-6 düzeylerinin yüksek olması da bu görüşü desteklemiştir (22).

COVID-19 hastalarının otopsi bulgularının incelendiği bir çalışmada, 4 hastada ölüm nedeninin masif pulmoner emboli olduğu ve tüm hastaların yarıdan fazlasında da tanı konulmamış derin ven trombozu (DVT) olduğu bildirilmiştir (23).

DVT, pulmoner emboli ve serebrovasküler komplikasyonlar gibi tromboembolik komplikasyonlar, çoklu organ yetmezliği ve artan mortalite ile ilişkilidir. Bu bağlamda pıhtılaşma aktivasyonu ve trombositopeni, COVID-19'de prognostik belirteçler olarak ortaya çıkmıştır (16).

Bizim çalışmamızda araştırmış olduğumuz 66 olgunun 40'ında (%60,6) komorbidite rapor edildi. Moleküler analiz sonuçlarına göre, 11 hastada (%16,7) heterozigot *FVL* genotipi saptandı ve bu heterozigotlar ile normal genotipte olan hastalar karşılaştırıldığında, tanı anında tespit edilen takipne ve hipotansiyon arasında anlamlı bir ilişki vardı. Sağlıklı Türk toplumunda *FVL* sıklığı %7,9'dur (%3,5-15) (24). Birçok çalışmada Türkiye'nin farklı yerlerinden venöz tromboemboli (VTE) geçirmiş Türklerde *FVL* prevalansı rapor edilmiştir. Türk toplumunda *FVL* ile ilişkili VTE riskini tahmin etmek için gerçekleştirilen ve 1202 VTE tanılı hasta ile 1283 sağlıklı kontrolün dahil edildiği bir meta-analiz çalışmasında, *FVL* görülme oranı VTE'li hastalarda (%22,8) kontrollere (%7,6) göre anlamlı derecede yüksek saptanmıştır (25). Literatürden başka bir çalışmada, *FVL* heterozigotluk durumunun, VTE riskini 5 ila 10 kat artırdığı ve *FVL* homozigotluk durumunun ise, bu riski normal popülasyona göre 80 ila 100 kat artırdığı gösterilmiştir (26). Literatürde yayımlanan birçok çalışmada, COVID-19 trombozu ve kalıtsal trombofili faktörleri arasında anlamlı ilişki olduğu da kanıtlanmıştır (27,28). Yakın zamanda, ülkemizde gerçekleşen, 9508 olgunun dahil edildiği çok merkezli retrospektif bir çalışmada, *FVL* ve *FII* mutasyonları ile COVID-19 hastalığının klinik bulguları arasındaki ilişki araştırılmış ve COVID-19 tanılı hasta grubunda tespit edilen tromboz sıklığının, COVID-19 olmayan gruba göre daha yüksek olduğu tespit edilmiştir. COVID-19 ile enfekte olan ve özellikle yoğun bakım ünitesinde tedavi gören kritik derecede ağır hastalarda trombozun arttığı görülmüştür. Aynı araştırmada; COVID-19 grubunda *FII* prevalansı daha yüksek ve istatistiksel olarak anlamlı, *FVL* prevalansı ise daha düşük bulunmuştur. Tromboz öyküsü olan COVID-19 hastalarında tespit edilen *FVL* mutasyonunun sıklığı, tromboz öyküsü olmayan COVID-19 hastalarına göre daha yüksek bulunmuştur. Çalışmalarında ayrıca, COVID-19 nedeniyle ölen hastalarda hem tromboz öyküsü varlığı hem de *FVL* mutasyonunun sıklığı daha yüksek bulunmuş fakat tromboz öyküsü ve *FII* mutasyonu arasında anlamlı bir ilişki bulunamamıştır. (13).

Bizim çalışmamızda, sigarayı halen kullanan hastalarda, sigarayı hiç içmemiş veya geçmişte bırakmış olanlara göre troponin düzeyleri daha yüksek tespit edildi (p=0,004). Yakın zamanda Türkiye'den gerçekleşen bir çalışmada, bizim çalışmamızın aksine troponin düzeyleri ve sigara kullanımı arasında bir ilişki olduğuna dair kanıt bulunamamıştır (29).

Yayımlanan bazı çalışmalarda, hem aktif sigara kullananlardan hem de geçmişte sigara içip bırakmış olan olgulardan elde edilen akciğer doku örneklerinde, nikotinik asetilkolin reseptörünün α-7 alt tipinin aracılık ettiği bir "ACE-2 ekspresyon yukarı doğru düzenlenmesi (up-regulasyon)" varlığı tespit edilmiştir (30-34). Literatürde diğer bir in vitro deneyin sonuçları, sigara içme öyküsü ile artan ACE-2 ekspresyonu arasında doza bağımlı bir korelasyon olduğunu doğrulamaktadır. Bu nedenle sigara içenlerin, artan ACE-2 ekspresyonu sonucunda daha yüksek SARS-CoV-2 yüklerine maruz kalması olasıdır ve bu durum, COVID-19'da sigara içmeye bağlı artan ciddi hastalık ve ölüm riski için mekanik bir açıklama sağlayabilir (35). Bu hipotez; bizim çalışmamızda, halen aktif sigara içen ve daha önceden sigara kullanmış olan 24 hastada, daha önce hiç sigara içmemiş olanlara göre istatistiksel olarak anlamlı düzeyde lenfopeni saptanmış olmasını açıklayabilir. Çünkü hücre yüzeyinde ACE-2 reseptörü bulunan lenfositlerin, bu reseptörlere oldukça güçlü bir şekilde tutunmak yoluyla giriş kapısı olarak kullanan ve yaşam döngüsünü başlatan SARS-CoV-2'nin hedefi olması olması ve hasar alması beklenmektedir (1). Çalışmamızda tespit edilen, COVID-19 hastalarında sigara içimi ve lenfopeni ilişkisinin tam anlamıyla açıklanabilmesinde, lenfopeniye yol açan potansiyel mekanizmaların ele alındığı daha ileri araştırmalara ihtiyaç duyulmaktadır.

Bu çalışmadan elde edilen en önemli sonuç, sigarayı halen kullanan hastalarda, sigarayı hiç içmemiş veya geçmişte bırakmış olanlara göre troponin düzeyleri daha yüksek tespit edilmiş olmasıdır (p=0,004).

Araştırmamızın bazı sınırlamaları bulunmaktadır. İncelenen hasta sayısının az olması araştırmanın şüphesiz en önemli sınırlamasıdır. Bunun dışında retrospektif olarak ve tek merkezli gerçekleşmesi de diğer sınırlamalardandır ve bu nedenle sonuçlar önyargılı olabilir. Örneklem büyüklüğünün geniş olmamasına rağmen, bu çalışmadan elde edilen bulguların, daha çok sayıda hastanın dahil edileceği geniş ölçekli çalışmalar açısından faydalı olacağını düşünüyoruz.

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Uncovering the Benefits of Epicatechin for Oxidative Stress in Human Health

İnsan Sağlığında Oksidatif Stres için Epikateşinin Faydalarının Ortaya Çıkarılması

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ABSTRACT

Objective: Epicatechin (EC) is one of the major components of green tea (*Camellia sinensis*) catechins. This study investigated the effect of the amount of epicatechin obtained by brewing green tea under optimal conditions against oxidative stress induced by hydrogen peroxide (H_2O_2). Materials and Methods: In peripheral blood mononuclear cells (PBMCs), the amount of epicatechin determined by brewing green tea under optimum conditions was applied against 250 µM H_2O_2 and cell viability was determined by 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test, total antioxidant status (TAS) levels and total oxidant status (TOS) levels were determined by biochemical analysis, apoptosis-related Bax, Bcl2, p53 expression analysis was determined by quantitative real time polimerase chain reaction (qRT-PCR) method. Results: The cell viability was significantly higher in the H_2O_2+EC group than in the H_2O_2 group ($p< 0.001$). TOS and TAS levels were changed considerably in the H_2O_2+EC group compared to the H_2O_2 group ($p<0.05$ and $p<0.001$, respectively). Bax, p53 expression level decreased in H_2O_2+epicatechin treated cells compared to H_2O_2 treated cells ($p<0.001$ and $p<0.01$ respectively), while Bcl2 expression level increased in H_2O_2+epicatechin treated cells compared to H_2O_2 treated cells $p<0.01$). Conclusion: The results show that the amount of epicatechin obtained from brewing green tea under optimum conditions has a protective effect on peripheral blood mononuclear cells (PBMCs) against H_2O_2 induced oxidative stress. Specifically, it was concluded that epicatechin increased cell viability, decreased oxidative stress markers and modulated the expression of key apoptosis-related proteins, thus promoting cell survival.

Keywords: *Bax, Bcl2, Epicatechin, Oxidative stress, p53*

ÖZ

Amaç: Epikateşin (EC) yeşil çay (*Camellia sinensis*) kateşinlerinin ana bileşenlerinden biridir. Bu çalışmada, yeşil çayın optimum koşullarda demlenmesiyle elde edilen epikateşin miktarının hidrojen peroksit (H_2O_2) tarafından indüklenen oksidatif strese karşı etkisi araştırılmıştır. Materyal ve Metot: Periferik kan mononükleer hücrelerinde (PBMCs), yeşil çayın optimum koşullarda demlenmesi ile belirlenen epikateşin miktarı 250 µM H_2O_2'ye karşı uygulanmış ve hücre canlılığı 3-(4, 5-dimetiltiyazol-2-yl)-2,5-difeniltetrazolyum bromür (MTT) testi ile, total antioksidan seviyeleri (TAS) ve total oksidan seviyeleri (TOS) biyokimyasal analiz ile, apoptoz ile ilişkili Bax, Bcl2, p53 ekspresyon analizi gerçek zamanlı kantitatif polimeraz zincir reaksiyonu (qRT-PCR) yöntemi ile belirlenmiştir. Bulgular: H_2O_2+EC grubunda hücre canlılığı H_2O_2 grubuna göre anlamlı derecede yüksek bulunmuştur ($p<0.001$). TOS ve TAS seviyeleri, H_2O_2 grubuna kıyasla H_2O_2+EC grubunda önemli ölçüde değişmiştir (sırasıyla $p<0.05$ ve $p<0.001$). Bax, p53 ifade düzeyi H_2O_2+epikateşin uygulanan hücrelerde H_2O_2 uygulanan hücrelere kıyasla azalırken (sırasıyla $p<0.001$ ve $p<0.01$), Bcl2 ifade düzeyi H_2O_2+epikateşin uygulanan hücrelerde H_2O_2 uygulanan hücrelere kıyasla artmıştır ($p<0.01$). Sonuç: Sonuçlar, yeşil çayın optimum koşullar altında demlenmesinden elde edilen epikateşin miktarının H_2O_2 kaynaklı oksidatif strese karşı periferak kan mononükleer hücreler (PKMH) üzerinde koruyucu bir etkiye sahip olduğunu göstermektedir. Spesifik olarak, epikateşinin hücre canlılığını artırdığı, oksidatif stres belirteçlerini azalttığı ve apoptozla ilgili anahtar proteinlerin ekspresyonunu modüle ettiği, böylece hücre sağ kalımını desteklediği sonucuna ulaşılmıştır.

Anahtar Kelimeler: *Bax, Bcl2, Epikateşin, Oksidatif stres, p53*

INTRODUCTION

Epicatechin EC is one of the main components of green tea catechins (1). Green tea has characteristics of meta-5,7-dihydroxy groups in chain A and dihydroxy or trihydroxy groups in chain B (2). The B chain seems essential to the antioxidant reactions (3). Antioxidant activity is a molecule or ion's capacity to prevent other molecules' oxidative reactions (4). EC has effective and direct antioxidant activity. By its strong antioxidant capacity, it scavenges free radicals in cells. Compared with vitamin C and vitamin E, the antioxidant capacity of EC is 20 and 50 times greater. The biological activity of ECs is mainly a result of interactions with proteins and lipids. These interactions result in an effect on the levels of oxidants (5).

Oxidative stress, characterised by an imbalance between free radicals and antioxidants, has a significant impact on several health conditions such as infertility, cancer, diabetes, metabolic syndrome, atherosclerosis, neurodegenerative, cardiovascular, gastrointestinal and liver diseases. H_2O_2 is a crucial reactive oxygen species (ROS) and plays a significant role in biological processes. Generally, when it exceeds 50 µM, it causes oxidative damage in tissues and organs and elicits an inflammatory response. Antioxidants are essential for neutralising free radicals and thus preventing oxidative damage. They can be enzymatic or non-enzymatic and work by scavenging free radicals, chelating metal ions or upregulating other antioxidant defences (6).

Green tea is considered one of the healthiest drinks around the globe. Its acceptance in this way is due to its rich structure in polyphenols (7, 8). While many studies have shown that plant-derived flavonoids have excellent antioxidant activity,(9, 10) research on green tea in recent years has focused on the relationship between consumption and disease prevention (7).

The catechins and sensory properties may differ depending on the green tea brewing conditions. Our aim with this study was to understand if the amount of epicatechin determined according to the optimum conditions during green tea brewing has a protective effect on cells against H_2O_2.

MATERIAL and METHOD

Isolation of Human PBMC

Peripheral venous blood was collected from heparin tubes from healthy volunteer who had not been exposed to radiation or any drugs or smoked for six months. The Declaration of Helsinki was followed in the study. This study was approved by the Süleyman Demirel University Medical Faculty Ethics Committee (decision dated 05.12.2023 and numbered 15/270). PBMCS were isolated by Histopaque 1077 (Sigma-Aldrich, Switzerland).
Cell viability was determined to be 98% using trypan blue stain. The medium was changed once every 24 hours (11). The workflow of the study is given in Figure 1.

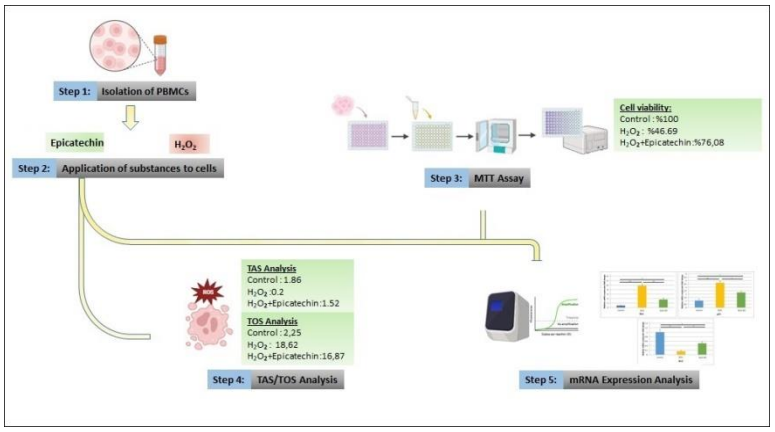

Figure 1: MTT assay, TAS-TOS levels and expression analyses after epicatechin and H_2O_2 treatment of cells

MTT Assay

PBMCs were seeded in 96-well flat-bottomed microplates (Sarstedt AG, Germany) at $1x10^4$ cells/well density. A 5% CO_2 incubator at 37 °C was incubated for 24 h before any treatments.

For the best result of taste and sensory properties, brewing at 85 °C for 3 minutes represents the optimal condition. Under these conditions, an epicatechin maximum of 6.75 mg/100 mL was determined (12). Epicatechin (Sigma Chemical Co., USA) of 67.5 ppm was cultured with cells in an incubator for 24 h (37 °C, 5% CO_2). During the last hour, these cells (except the control group) were incubated with 250 µM H_2O_2 (13).

The medium consisted of the following components: RPMI-1640 (Biological Industries, Israel) medium, 10% FBS (Sigma - Aldrich, USA) and 100 IU/mL penicillin, 100 µg/mL streptomycin (Sigma - Aldrich, USA). MTT (Sigma, USA) final concentration was adjusted to 0.5 mg/mL. The resulting formazan crystals were dissolved in DMSO. A multiscan plate reader (Synergy HTX BioTek, USA) was used to measure cell viability at 570 nm (14). Cell viability was evaluated in percentage relative to the control group, denoted as 100%. Three individual wells were measured per treatment point.

Biochemical Analysis

After the culture step, plates were centrifuged at 1800g for 6 minutes, and the pellet was washed with PBS. An ultrasonic homogenizer was used to homogenize the cells. After the second centrifugation, supernatants were transferred to Eppendorf tubes for analysis (15).
TAS and TOS levels were measured by spectrophotometric method (Beckman Coulter AU 5800, USA) in triplicate with commercial kits (Rel Assay Diagnostics, Türkiye) according to the kit protocol (16). The results were expressed as millimolar Trolox equivalents per liter in TAS and micromolar hydrogen peroxide equivalent per liter (µmol H_2O_2 Eqv/L) in TOS (17).

RT-qPCR Analysis on mRNA

Total RNA extraction, purity and concentration measurement, cDNA extraction were performed similar to our previous study and according to the manufacturer's protocol (18). Primers were designed to detect specific mRNA sequences. The NCBI website was used to test possible primer sequences. Bax (F:5′-CAGGGGCCCTTTTGCTTCA-3′ R:5′-GGAAAAAGACCTCTCGGGGG-3′), Bcl-2 (F:5′-AAAAATACAACATCACAGAGGAAGT-3′ R:5′-TCCCGGTTATCGTACCCTGT-3′), p53 (F:5′-ACCTATGGAAACTACTTCCTGAAA-3′ R:5′-GCTGCCCTGGTAGGTTTTCT -3′) primers were designed to amplify. ACTB (F: 5′-GCCTCGCCTTTGCCGAT-3′ R:5′- AGGTAGTCAGTCAGGTCCCG-3′) expression was used for normalization. The manufacturer's instructions were followed for real-time RT-PCR conditions. The $2^{-\Delta\Delta Ct}$ comparative method was used for relative quantification of gene expression. To determine amplification specificity, qPCR products were evaluated using melting curves. Each sample was run in triplicate.

Statistical Analysis

The results of the expression study were evaluated using SPSS 18.0 statistical analysis software (SPSS Inc., Chicago, IL). One-way ANOVA was used to analyze the results of the expression, MTT, TAS, and TOS levels. LSD and TUKEY tests were used as post-hoc tests. $p<0.05$ was considered to be significant.

RESULTS

MTT Assay Results

Cell viability was significantly lower in the H_2O_2 and H_2O_2+epicatechin groups compared with the control group ($p<0.001$). In the comparison of cell viability in the H_2O_2 group and the H_2O_2+epicatechin group, the H_2O_2+epicatechin group was significantly higher ($p<0.001$) (Figure 2).

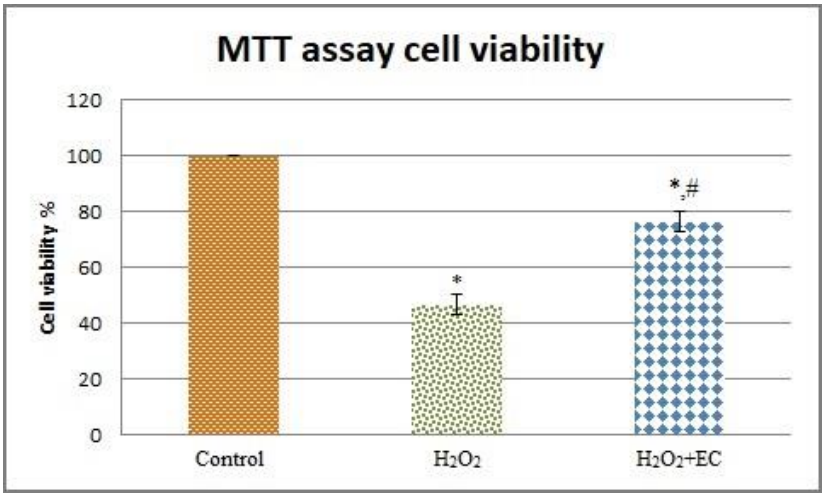

Figure 2: Cell viabilty. Data expressed as mean±SD. Comparision between groups and result were assessed by one-way ANOVA test. *p<0.001 ascompared to the control group, #p<0.001 compared to the H_2O_2-treated group.

Biochemical Results

TOS level was significantly higher in the H_2O_2 and H_2O_2+epicatechin groups than in the control group (p<0.001). TOS level was considerably higher in the H_2O_2 group than in the H_2O_2+epicatechin group (p<0.05). TAS level was significantly lower in the H_2O_2 group than in the control group (p<0.001) and considerably higher in the H_2O_2+epicatechin group (p<0.001). TAS level was significantly higher in the H_2O_2+epicatechin group than in the H_2O_2 group (p<0.001) (Table 1).

Table 1: TOS and TAS levels of PBMCs

Groups	Negative Control	H_2O_2	H_2O_2+EC
TOS (μmol H_2O_2 Eq./L)	2.25±0.74	18.62±0.82*	16.87±0.53*,#
TAS (mmol TroloxEq./L)	1.86±0.08	0.20 ± 0.04*	1.52± 0.04*,##
OSI (μmol $H2O_2$ equiv./lt)/(mmol Trolox equiv./lt x 10)	0.12±0.04	9.36±1.49	1.11±0.02

Data are expressed as mean±SD. One-way ANOVA test was used to assess comparisons between groups and results of oxidative stress markers. LSD tests were used as post-hoc tests. *p<0.001 compared to the control group; #p<0.05, ##p<0.001 compared to the H_2O_2 treated group.

Expression Analysis of Bax, Bcl, p53

The relative mRNA level of Bax in the H_2O_2, H_2O_2+epicatechin groups increased significantly compared to the control group (respectively; p<0.001 and p<0.01) and lower significantly in H_2O_2+epicatechin group compared to the H_2O_2 group (p<0.001). The relative mRNA level of p53 in the H_2O_2, H_2O_2+epicatechin groups increased significantly compared to the control group (respectively; p<0.001 and p<0.01) and lower significantly in H_2O_2+epicatechin group compared to the H_2O_2 group (p<0.01). The relative mRNA level of Bcl-2 in the H_2O_2, H_2O_2+epicatechin groups decreased significantly compared to the control group (respectively; p<0.001 and p<0.01) and lower significantly in H_2O_2+epicatechin group compared to the H_2O_2 group (p<0.01) (Figure 3).

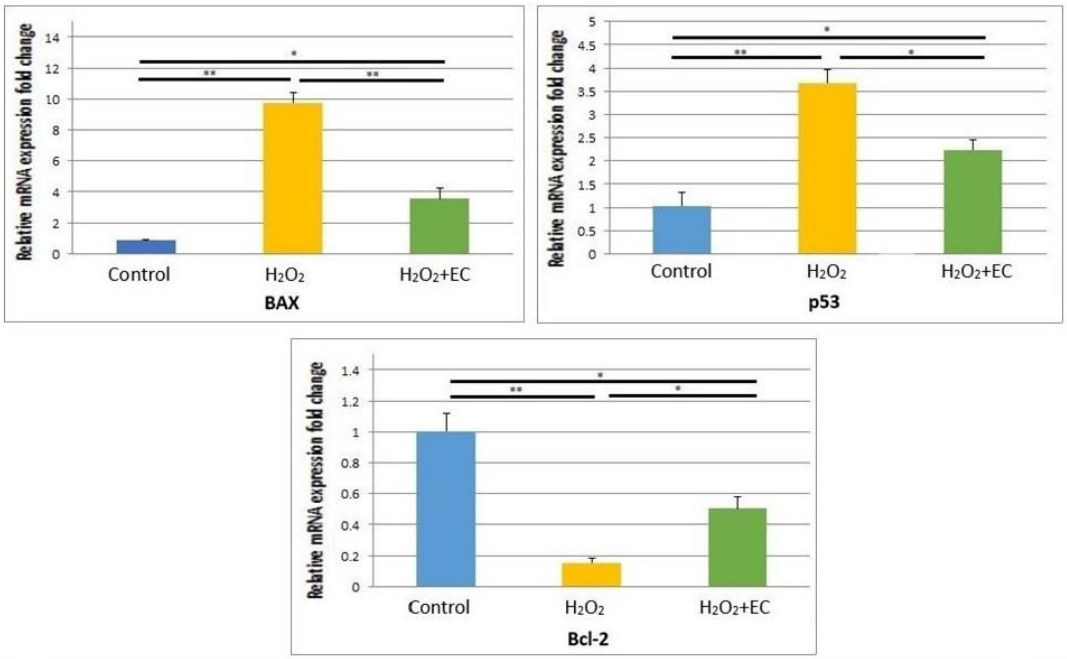

Figure 3: Relative Mrna Expression Results And Statistical Comparison Between Groups.
Bax: Bcl-2-associated X protein; p53: Tumor Protein P53; Bcl2: B-cell lymphoma 2;Values are presented as means±SD. *p<0.01, **p<0.001.

DISCUSSION and CONCLUSION

PBMCs, consisting mainly of lymphocytes and monocytes, are a readily available blood cell fraction with high research potential for testing the effects of dietary intake. At the gene expression level, they reflect the impact of environmental changes. Many studies demonstrated the utility of PBMCs in showing the effects of nutrition, training, and vigorous exercise on mitochondrial oxidative balance, biosynthesis, dynamics, and antioxidant capabilities (19,21). In this context, PBMCs were considered more appropriate for our research.

Oxidative stress is the result of an imbalance between free radicals and antioxidants. It causes changes in the structure of cell membranes, lipids, proteins, lipoproteins, and DNA. Mitochondria are the most important endogenous source of ROS generation, as they play a role in forming ATP through oxidative phosphorylation, which reduces molecular O_2 to H_2O via the electron transport chain (22). A study showed that heavy exercise enhances the oxidative stress-induced apoptosis (23). Another study demonstrated that exopolysaccharide-selenium nanoparticles promoted cell survival by maintaining over 90% cell viability under oxidative stress caused by 0.4 mM H_2O_2 in HepG2 cells (24). H_2O_2 is a source of reactive oxygen species, and functions act to induce oxidative stress (25). H_2O_2 is commonly considered a cytotoxic substance that must be reduced by antioxidant defense enzymes (26).

An ex-vivo study has suggested that green tea consumption prevents LDH oxidation in humans, while Epicatechin also plays a role in the prevention of neurodegenerative diseases such as Alzheimer's and Parkinson's (27). In addition, in an in vivo study, tea catechins were observed to reduce the formation of atherosclerosis in mice with apolipoprotein E deficiency (28), while another study found that the antioxidant capacity of epicatechin in human plasma increased by 40% compared to non-users (29).

Our results show that the treatment with H_2O_2 led to a significant decrease in the viability of the PBMCs. However, epicatechin had a protective effect on cell viability when used against H_2O_2, which causes oxidative stress. In addition, our results showed that the H_2O_2-induced increase in TOS levels in PBMCs decreased with epicatechin treatment, while TAS levels increased.

In a study, it was found that after treatment of mouse granulosa cells and human granulosa cells with H_2O_2, the viability rate of the cells decreased with concentration, while the expression levels of p53 and Bax increased. These findings suggest that H_2O_2-oxidative stress may be a factor in the onset of apoptosis. Because when DNA damage is limited and reversible, cells stop proliferating. Some cells exposed to DNA damage enter the cell cycle. However, when DNA damage is irreparable, cells undergo immediate apoptosis, thereby causing induction of p53 and p21 expression (30). In another study, (-)-epicatechin was found to upregulate death receptors (DR4/DR5) and modulate pro-apoptotic proteins in MDA-MB-231 cells. In contrast, it did not activate the death receptor in MCF-7 cells (31).

Similar to the studies conducted with cell culture in the literature, in our research, Bax, p53 expression increased while Bcl2 expression decreased in cells treated with H_2O_2 only compared to control cells. In H_2O_2+EC treated cells, Bax, p53 expression decreased while Bcl2 expression level decreased compared to the H_2O_2 group. Bax, p53, and Bcl2 genes networks and functions are present in Figure 4 (https://genemania.org/).

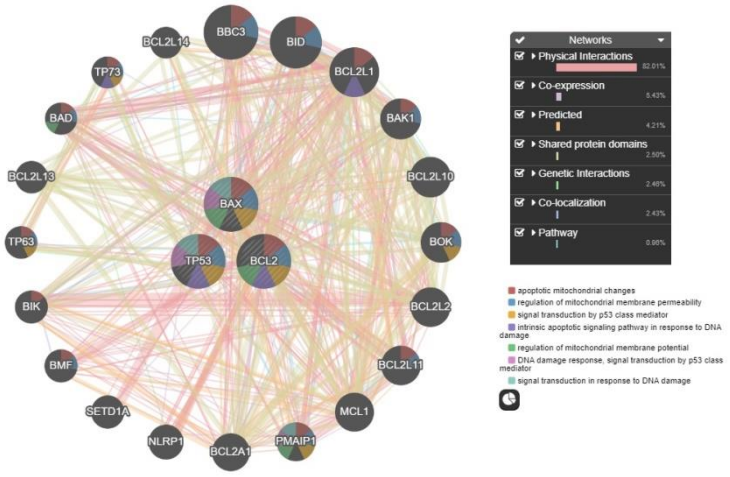

Figure 4: Bax, p53, Bcl2 genes networks and functions

The mechanisms of action of natural antioxidants are unclear. Further research is needed to identify the active target sites. In this direction, in our study, the mechanism by which the amount of epicatechin determined by brewing green tea under optimal conditions plays a protective role against H_2O_2-induced oxidative stress was revealed by genetic and biochemical tests. However, in addition to cellular studies, it is thought that the amount of epicatechin obtained by brewing and consuming green tea under optimal conditions will be insufficient to reduce the effects of oxidative stress in people who exercise excessively. We believe that this study may provide a basis for in vivo studies.

Declaration of Ethical Code: In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

This study was approved by the Süleyman Demirel University Medical Faculty Ethics Committee (decision dated 05.12.2023 and numbered 15/270).

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Psoriatik Artritte Sekukinumab Klinik Deneyimi ve Enflamatuar Parametrelerin Değerlendirilmesi

Clinical Experience with Sekukinumab and Evaluation of Inflammatory Parameters in Psoriatic Arthritis

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ÖZ

Amaç: Sekukinumab İnterlökin-17A' ya bağlanan insan immünoglobulin G1 kappa monoklonal antikorudur. Bu çalışmada sekukinumab tedavisi kullanan psöriyatik artrit (PsA) hastalarının dermografik, klinik ve inflamatuvar paremetrelerini, tedaviye devam sürelerini ve yan etki profilini değerlendirmeyi amaçladık. Materyal-Metot: Çalışmaya 2006 CASPAR sınıflandırma kriterlerine göre PsA tanısı almış ve sekukinumab tedavisi kullanan hastalar dahil edildi. Tedavinin etkinliği ve güvenliği değerlendirildi. İlaç sağkalımı analiz edildi. Tedavi öncesi ve sonrası monosit/lenfosit oranı (MLO), nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), sistemik immün inflamasyon indeksi (SII) (trombosit sayısı x nötrofil sayısı/ lenfosit sayısı), sistemik inflamatuvar cevap indeksi (SIRI) (nötrofil sayısı x monosit sayısı / lenfosit sayısı) inflamatuvar paremetreleri hesaplandı. Bulgular: Çalışmaya dahil edilen 41 PsA hastasının 45 ay süresince 29 (%70,7)' unun sekukinumab tedavisine devam ettiği görüldü. Hastaların 12 (%29,3) tedaviyi bıraktı. Tedaviyi en sık bırakma nedeninin ilaç etkisizliği olduğu, yan etki olarak da dispeptik yakınmalar ve gastrointestinal yan etkiler olduğu tespit edildi. Tedavi öncesi ve sonrasında bakılan inflamatuvar paremetrelerde istatiksel olarak anlamlı bir farklılık saptanmadı. Sonuç: Çalışmamızda hastaların büyük bir kısmında daha önce bir biyolojik ajan kullanmış olmasına rağmen sekukinumab tedavisinde kalım oranlarının oldukça yüksek olduğu saptanmıştır. Tedavi altında iken mortaliteyi artıran herhangi bir yan etki görülmemiştir. Sekukinumab, PsA tedavisinde etkili bir tedavi seçeneği olarak klinik kullanımımızda yer almaktadır.

Anahtar Kelimeler: *Sekukinumab, İnterlökin-17A, Psöriyatik artrit*

ABSTRACT

Objective: Secukinumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to Interleukin-17A. The objective of this study was to evaluate the dermographic, clinical and inflammatory parameters, treatment duration and side effect profile of patients with psoriatic arthritis who were treated with secukinumab. Material-method: Patients diagnosed with PsA according to 2006 CASPAR classification criteria and receiving secukinumab treatment were included in the study. The efficacy and safety of the treatment were evaluated. Drug survival was analyzed. The pre- and post-treatment monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune inflammation index (SII) (platelet count x neutrophil count / lymphocyte count), and systemic inflammatory response index (SIRI) (neutrophil count x monocyte count / lymphocyte count) were calculated as inflammatory parameters. Results: Of the 41 patients with PsA who were included in the study, 29 (70.7%) continued with secukinumab treatment for 45 months. Twelve patients (29.3%) discontinued treatment. The most common reason for discontinuation was drug ineffectiveness, and dyspeptic complaints and gastrointestinal side effects were found to be side effects. No statistically significant difference was identified in the inflammatory parameters analysed before and after treatment. Conclusion: In the present study, despite the fact that the majority of patients had previously undergone treatment with a biological agent, the survival rates observed in those receiving secukinumab were found to be relatively high. No side effects that increased mortality were observed during treatment. Secukinumab is currently being employed in clinical practice as an efficacious treatment option for the management of PsA.

Keywords: *Secukinumab, Interleukin-17A, Psoriatic arthritis*

GİRİŞ

Psöriyatik artrit (PsA) artrit, spondilit, daktilit, entesit, sedef hastalığı ve tırnak hastalığı dahil olmak üzere çok çeşitli semptomlarla karakterize, kas-iskelet sistemini tutan kronik inflamatuar bir hastalıktır (1, 2). PsA' nın patogenezi çok yönlü olup genetik yatkınlık, çevresel faktörler, doğal ve kazanılmış bağışıklık aktivasyonu arasındaki etkileşim sonrasında ortaya çıkan otoinflamasyon gibi çeşitli faktörler patogenezde rol oynamaktadır. Yapılan çalışmalar sonucunda TNF, İnterlökin-23 (IL-23), IL-17 gibi sitokinlerin rol aldığı immün-inflamatuvar yolaklar hastalık patogenezinde tanımlanmıştır (3).

PsA' da farmakolojik tedavi olarak non-steroid antiinflamatuvar ilaçlar (NSAID) ve metotreksat (Mtx) gibi geleneksel hastalık modifiye edici sentetik anti-romatizmal ilaçlar (csDMARD) kullanılır (2,4). Son yıllarda, biyolojik DMARD' ların (bDMARD) kullanımı ile PsA tedavisinde önemli değişiklikler meydana gelmiştir (2). Bu grupta ilk önce hastalık patogenezinde TNF-α majör etkisinden dolayı TNF-α inhibitörleri (TNFi) kullanılmıştır. Daha sonra TNF-α' nın yanında IL-12, IL-17, IL-23 gibi diğer proinflamatuvar sitokinlerin de PsA' nın patogenezinde rol oynadığı anlaşılmasıyla birlikte hedefe yönelik tedaviler geliştirilmiştir. Hastaların sinoviyal sıvısında ve ciltte IL17-A nın tespit edilmesi ve hastalığın ve ekstraartiküler bulguların patogenezinde IL-17A nın rolünün anlaşılması anti-IL-17 tedavisi geliştirilmesine sebep olmuştur. Sekukinumab, yüksek afiniteli IL-17A' yı hedefleyen insan monoklonal rekombinant bir antikordur (5). FUTURE-3 çalışmasında, NSAID' ler, bDMARD' lara rağmen aktif hastalığı olanlarda 150 veya 300 mg sekukinumab, plaseboya kıyasla PsA' nın klinik belirti ve semptomlarını düzelttiği görülmüştür (6). FUTURE 1 ve 5 'te sekukinumabın yapısal eklem hasarını engellediği görülmüş ve 1-3 yıllık tedavi boyunca düşük radyografik ilerleme oranlarıyla ilişkilendirilmiştir (7,8). Adalimumab ile bire bir karşılaştırmalı çalışmada sekukinumab, eklem bulgularında adalimumab' a benzer etkinlik göstermiştir (9). Sonuç olarak, sekukinumab PsA tedavisinde etkilidir ve genellikle iyi tolere edilir bir tedavidir. Dolayısıyla aktif PsA' lı yetişkin hastalarda özellikle cilt bulguları baskın hasta grubunda ilk tedavi seçeneği olarak tercih edilmesi önerilmektedir. Aktif PsA' lı yetişkin hastaların tedavisi için birçok ülkede kullanım onayı mevcuttur (5).

PsA kronik immün aracılıklı inflamatuvar bir hastalık olduğu için nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), monosit/lenfosit oranı (MLO), sistemik immün inflamasyon indeksi (SII), sistemik inflamatuvar cevap indeksi (SIRI) gibi inflamatuvar parametreler yüksek olması beklenmektedir. Özellikle inflamasyonun yüksek olduğu aktivasyon döneminde inflamatuar belirteçler ve indeksler yüksek tespit edilmektedir. Yapılan bir çalışmada NLO ve PLO' nun PsA olan hastalarda daha yüksek olduğu, NLO' nun hastalık aktivitesiyle ilişkili olduğu ve 12 aylık immünsüpresif tedavi ile iki parametrenin de gerilediği gösterilmiştir (10). Ayrıca psöriyazisli hastalarda yapılan bir çalışmada SII ve SIRI yüksek olduğu gösterilmiştir. Başka bir çalışma da tedavi ile NLO, PLO, SII değerlerinde gerileme olduğu saptanmıştır (10,11).

Bu çalışmada, sekukinumab kullanılan PsA hastalarında tedavi yanıtı, tedavide kalım oranları ve inflamatuar belirteçlerindeki değişim oranlarını tespit etmeyi amaçladık.

GEREÇ ve YÖNTEM

Çalışmamızda, Romatoloji Bölümünde Ocak 2020-Haziran 2023 tarihleri arasında, 2006 CASPAR sınıflandırma kriterlerine göre PsA tanısı almış ve en az bir kez sekukinumab tedavisi kullanılan 50 hastanın verileri retrospektif olarak değerlendirildi. 9 hasta takipsiz olduğu için çalışma dışı bırakıldı. 41 hasta çalışmaya dahil edildi. Hastalara ait demografik veriler, klinik özellikler, tedavide kalım süreleri ve tedaviyi bırakma nedenleri kaydedildi.

Dahil edilme kriterleri:
1. PsA ile takip edilen ve sekukinumab tedavisi alan 18 yaş ve üzeri hastalar
2. Sekukinumab tedavisini en az 6 ay kullanmış olmak
3. Romatoloji bölümünde takipli olmak
4. Tedavi öncesi ve sonrası sosyo-demografik verileri, klinik ve laboratuvar bulguları alınan hastalar.

Dışlama kriterleri:
1. Sekukinumab tedavisini 6 aydan önce bırakmış olmak
2. Tedavi öncesi ve sonrası sosyodemografik verileri, klinik ve laboratuvar bulgularına erişilemeyen hastalar

Tedavide kalım süresi en az altı ay olan hastaların tedavi başlangıcı, tedavinin üçüncü ve altıncı ayında bakılan inflamatuvar parametreleri kaydedildi. İnflamatuvar parametreler: NLO, PLO, MLO, SII, SIRI kullanıldı. NLO, PLO, MLO değerlerin birbirine oranlaması ile hesaplandı. Sistemik immün inflamasyon indeksi; trombosit sayısı x nötrofil sayısı/ lenfosit sayısı, sistemik inflamatuvar cevap indeksi; nötrofil sayısı x monosit sayısı / lenfosit sayısı şeklinde hesaplandı.

Veriler Windows IBM SPSS yazılım sürümü 25.0 kullanılarak (SPSS, Chicago,IL,ABD) analiz edilmiştir. Kategorik veriler frekans ve yüzde olarak; kantitatif veriler ise ortanca, minimum ve maksimum değerler verilerek özetlenmiştir. Bağımlı gruplar karşılaştırılırken Wilcoxon testi kullanılmıştır. $P<0,05$ olması istatistiksel olarak anlamlı kabul edilmiştir.

BULGULAR

Kliniğimizde sekukinumab tedavisi 41 PsA hastasına başlanıldı. Tedavi alan hastaların 33 (%80,5)' ü kadındı. Hastaların yaş ortalaması 49,2 ± 11,1 yıl olarak hesaplandı. Tedavi başlanan hastaların ortanca psöriyazis süresi 15 yıl, PsA süresinin 9 yıl olarak bulundu. Poliartiküler tutulumun 15 (%36,6), oligoartiküler tutulumun 21 (%51,2), aksiyel tutulumun 5 (%12,2) hasta daolduğu saptandı. Hastaların 13 (%31,7)' ünde daktilit, 10 (%24,4)' unde entezit, 20 (%48,8)'sinde tırnak değişikliği görüldü. Mtx (%90,2) En çok kullanılan konvansiyonel DMARD idi. Bir hastanın sülfasalazin, 14 hastanın Mtx+lef, 3 hastanın leflunomid, 10 hastanın Mtx+lef+sülfasalazin kullandığı saptandı. Biyolojik ajan naif olan üç hasta (%7,3) mevcut idi. Daha önceden en az bir biyolojik tedavi alan 38 hasta tespit edildi. Medyan sekukinumab kullanım süresi 16 (1-45) aydır. Hastaların medyan steroid dozu 7,5 (0-16) mg olarak hesaplandı. Hastaların 29 (%70,7)' unun tedaviye devam ettiği, 12 (%29,3)' sinin de tedaviyi sonlandırdığı görüldü. romatoid faktör (RF) değeri pozitif olan 2 hasta (%4.9) saptandı (Tablo 1).

On iki hastanın ilacı bırakma nedeni incelendi. Bir hasta pnömoni, 1 hasta pelvik inflamatuvar hastalık (PIH), 3 hasta gastrointestinal yan etki, 2 hasta inflamatuvar barsak hastalığı aktivasyonu (İBH), 1 hasta gebelik, 1 hasta tedavi uygulamada zorluk nedeniyle tedaviyi bıraktı. Üç hastada ilaç etkisizliği saptanarak tedaviyi sonlandırdı.

Biyolojik naif olmayan 38 hasta (%92,7) mevcut idi. Psöriyazis nedeniyle sekukinumab başlanılan 3 (%7,3) hasta ise biyolojik naifti. Biyolojik naif olan hasta sayısının azlığı nedeniyle iki grup arasındaki karşılaştırma istatiksel olarak anlamlı değildir.

Tedaviye devam eden 25 hastanın inflamatuvar indeksleri kaydedildi. SII tedavi başlangıcı 661,52±655,66, tedavinin üçüncü ayında 605,88±375,58, tedavinin altıncı ayında 617,56±497,76 idi. SIRI tedavi başlangıcında 1,32±1,00, tedavinin üçüncü ayında 1,28±0,79, tedavinin altıncı ayında 1,13±0,61 idi. NLO tedavi başlangıcında 2,47±1,82, tedavinin üçüncü ayında 2,17±0,82, tedavinin altıncı ayında 2,33±1,07 idi. MLO tedavi başlangıcında 0,25±0,12, tedavinin üçüncü ayında 0,28±0,15, tedavinin altıncı ayında 0,30±0,25 idi. PLO tedavi başlangıcında 137,52±63,81,

tedavinin üçüncü ayında 151,24±76,61, tedavinin altıncı ayında 153,20±86,96 idi. CRP tedavi başlangıcında 5,39±4,69, tedavinin üçüncü ayında 5,56±4,80, tedavinin altıncı ayında 6,06±3,29 idi. ESR tedavi başlangıcında 17,76±15,54, tedavinin üçüncü ayında 13,72±13,46, tedavinin altıncı ayında 13,76±9,62 idi. Hastaların tedavi başlangıcında, tedavinin üçüncü ayında ve altıncı ayında bakılan NLO, PLO, MLO, SII, SIRI arasında istatiksel olarak anlamlı bir fark saptanmadı (Tablo 2).

Tablo 1: Sekukinumab Kullanan Hastaların Demografik Özellikleri

	Tüm hastalar (n=41)	Sekukinumab devam (n=29)	Sekukinumab kesilen (n=12)	p
Kadın, n (%)	33 (%80,5)	23 (%79,3)	10 (%83,3)	1,000
Yaş, yıl, (ort, min-max)	49,2 (24-70)	50 (24-70)	45(29-59)	0,800
Psöriyazis süresi, yıl (ort, min-max)	15 (2-40)	13 (2-33)	21 (6-40)	0,228
PsA süresi, yıl, (ort,min-max)	9 (1-30)	8 (1-30)	11 (4-30)	0,442
Tutulum tipi, n (%)				
Poliartiküler	15 (%36,6)	11 (%37,9)	4 (%33,3)	
Oligoartiküler	21 (%51,2)	15 (%51,7)	6 (%50)	
Aksiyel	5 (%12,2)	3 (%10,3)	2 (%16,7)	
Daktilit	13 (%31,7)	6 (%20,7)	7 (%58,3)	
Entezit	10 (%24,4)	6 (%20,7)	4 (%33,3)	
Tırnak değişikliği, n (%)	20 (%48,8)	15 (%51,7)	5 (%41,7)	0,808
Tedavi, n (%)				
Mtx	10 (%24,4)	8 (%27,6)	2 (%16,7)	
Lef	3 (%7,3)	3 (%10,3)	0 (%0)	
Mtx- Lef	14 (%34,1)	8 (%27,6)	6 (%50)	
Mtx-Slz	3 (%7,3)	3 (%10,3)	0 (%0)	
Mtx-Slz- Lef	10 (%24,4)	6 (%20,7)	4 (%33,3)	
Slz	1 (%2,4)	1 (%3,4)	0 (%0)	
Sekukinumab tedavi, ay, (ort, min-max)	16 (1-45)	29 (2-45)	12 (1-38)	0,637
Biyolojik naif, n (%)	3 (%7,3)	3 (%10,3)	0 (%0)	0,680
Steroid, mg, (ort, min-max)	7,5 (0-16)	6,4 (0-16)	10 (4-16)	0,109
RF pozitif, n (%)	2 (%4.9)	2 (%6.9)	0 (%0)	1,000

Cdmard; konvansiyonel hastalık modifiye edici antiromatizmal ilaç, mtx: metotreksat, min; minimum, max; maksimum, lef; leflunomid, ort; ortalama, psa; psöriyatik artrit, rf: romatoid faktör, slz: sülfasalazin.

Tablo 2: Sekukinumab Tedavisi Altında Hastaların Enflamatuvar Paremetreleri

	Tedavi Başlangıcı (ort, ss)	Tedavinin 3. Ayı (ort, ss)	Tedavinin 6. Ayı (ort, ss)	p
SII	661,52±655,66	605,88±375,58	617,56±497,76	0,906
SIRI	1,32±1,00	1,28±0,79	1,13±0,61	0,208
NLO	2,47±1,82	2,17±0,82	2,33±1,07	0,662
MLO	0,25±0,12	0,28±0,15	0,30±0,25	0,291
PLO	137,52±63,81	151,24±76,61	153,20±86,96	0,226
CRP	5,39±4,69	5,56±4,80	6,06±3,29	0,083
ESR	17,76±15,54	13,72±13,46	13,76±9,62	0,067

CRP; c-reaktif protein, ESR; eritrosit sedimantasyon hızı, MLO; monosit/lenfosit oran, NLO; nötrofil/lenfosit oranı, ort; ortalama, PLO; platelet/lenfosit oranı, SII; sistemik immün inflamasyon indeksi (trombosit sayısı x nötrofil sayısı/ lenfosit sayısı), SIRI; sistemik inflamatuvar cevap indeksi (nötrofil sayısı x monosit sayısı / lenfosit sayısı), ss; standart sapma.

TARTIŞMA ve SONUÇ

Çalışmamız PsA hastalarında sekukinumab tedavisinin etkinliğinin, ilaca devam durumunun ve inflamatuvar paremetrelerin değerlendirildiği tek merkezin gerçek yaşam deneyimidir.

Sekukinumab tedavisinde kalım süresi ilk bir yılda literatürde AS ve PsA %55 ile %86 arasında değişmektedir (12–15). Bizim çalışmamızda 41 hastanın 10 tanesine son bir yıl içinde tedavi başlanmıştır. 31 hastanın ise bir yıllık tedavide kalım oranı %61 olarak kaydedilmiştir. Bu oran literatürle benzer aralıkta olup, literatürde bahsi geçen yüksek kalım oranlarına ulaşılamamasının nedeni ise, tedavi başlanılan grubun birçoğunun TNF'i naif olmaması ve dirençli hasta grubu olması ile ilişkilendirildi. ASTURias çalışması gibi literatürdeki birçok çalışmada, TNFi dirençli grupta, TNFi naif gruba göre tedavide kalım süresi daha az olduğu görülmüştür (14,15). PsA sınıflama kriterlerinden biri RF negatifliği olsada, yapılan çalışmalarda PsA olan hastalarda yaklaşık %8,3-11 oranında artmış RF prevelansından bahsedilmektedir (16,17). Bizim çalışmamızda ise bu oran %4,9 olarak bulunmuştur.

Sekukinumab kullanımı ile mukokutanöz kandida enfeksiyonları, üst solunum yolu enfeksiyonu, nazofarenjit ve gibi enfeksiyöz durumlara yatkınlığı artırabilmektedir. Çalışmaya alınan hastalardan bir hasta pnömoni bir hasta da PIH nedeniyle ilacı bıraktı (5). Hasta sayısının az olması nedeniyle bu veriyi literatür ile karşılaştırmak uygun değildir.

Sekukinumab ile İBH arasındaki ilişkiyi araştıran bir çalışmada 1380 hastada değerlendirilmiş. 7 hastada yeni başlangıç olmak üzere 8 hastada İBH tespit edilmiştir (18). Çalışmamızda 2 hastada İBH aktivasyonu görüldü ve tedavi sonlandırıldı. Hasta sayısının az olması nedeniyle yapılan çalışmaya oranla daha yüksek bir oranda kliniğimizde İBH aktivasyonu görüldü. Bu durum hasta sayısının yetersiz olması ile ilişkilendirildi.

Sekukinumab tedavisi alan hastalarda yapılan tüberküloz (TB) reaktivasyonu çalışmasında aktif TB veya latent TB enfeksiyonu reaktivasyonu vakası bildirilmemiştir. Bizim takipli hstalarımızda da TB reaktivasyonu görülmemiştir (19).

Günümüzde birçok çalışmada hematolojik parametrelerden hesaplanan bazı indeksler sistemik inflamasyonun göstergesi olarak birçok alanda kullanılmaktadır. Çalışmamızda bakılan NLO, MLO, PLO, SII, SIRI oranlarının birçok çeşitli çalışmada inflamasyon durumlarında arttığı doğrulanmıştır (20, 21, 22, 23). Crp ve ESH düzeyleri PsA hastalarında inflamasyonun bir göstergesi olarak yüksek bulunabilir (24,25). PsA ve ankilozan spondilit (AS) hastalarında yapılan bir çalışmada sekukinumab tedavi başlangıcı ve altıncı ayda bakılan hemogram değerlerinde, CRP ve ESH düzeylerinde anlamlı bir fark saptanmamıştır (26). TNFi ve sekukinumab kullanan iki grup arasında yapılan başka bir çalışmada NLO ve PLO oranları bakılmış olup sekukinumab alan grupta daha yüksek bulunmuştur (27). Psöriyazisde yapılan bir çalışmada sekukinumab tedavisi sonrası CRP, NLO ve PLO' da düşüş olduğu görülmüştür (28). Kırk dört hasta üzerinde yapılan başka bir çalışmada CRP değerlerinde anlamlı düşüş saptanmazken, ESH değerlerinde düşüş saptanmıştır (29). Bu konuda literatürde çelişkili sonuçlar mevcuttur. Tedavi ile inflamatuvar parametrelerde anlamlı azalma olduğunu gösteren çalışmalar mevcut olamasına rağmen herhangi bir fark olmadığını belirten de yayınlar mevcuttur. Ancak sekukinumab ile ilgili 5' i PsA olmak üzere (2475 hasta) 19 klinik çalışmanın (9197 hasta) analiz edildiği bir derlemede tedavinin 16. haftasında PsA hastalarında CRP ve NLO' da anlamlı bir düşüş olduğu görülmüştür (30). Ancak bizim çalışmamızda herhangi inflamatuvar bir parametrede düşüş saptanmamıştır.

Çalışmamızın temel kısıtlılığı inflamasyon belirteçlerinin sadece hastalık klinik olarak remisyonda olduğu dönemde bakılması ve hastalık aktivite skorları ile birlikte değerlendirilmemesi, kesitsel bir çalışma olması, hasta sayısının az olmasıdır. Buna bağlı olarak inflamatuvar parametrelerde anlamlı bir fark görülmediği düşünülmektedir.

Sekukinumab, TNFi kullanmamış ve TNFi dirençli PsA hastalarında güvenli ve etkilidir (6,7, 8). Çalışmamızda ortanca 16 aylık takip süresinde ciddi malignite ve mortalite görülmemiştir. Bu durum mevcut literatürle uyumludur. Çalışmamızda hastaların büyük bir kısmında daha önce bir biyolojik ajan kullanmış olmasına rağmen sekukinumab tedavisinde kalım oranlarının oldukça yüksek olduğu saptanmıştır. Sekukinumab, PsA tedavisinde etkili bir tedavi seçeneği olarak klinik kullanımımızda yer almaktadır.

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Fetal Dose in CT Scans During Pregnancy

Hamilelikte BT ile Fetal Doz Değerlendirmesi

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ABSTRACT

Objective: In cases where computed tomography (CT) scans are clinically necessary for pregnant patients, accurately estimating fetal radiation exposure is essential. Current methods, however, lack practicality for routine clinical use. This study aims to calculate fetal and organ doses in pregnant patients undergoing CT scans using the Monte Carlo Simulation Method. Methods: Monte Carlo (MC) simulations were conducted on phantoms representing pregnant patients at gestational ages of 8-15 weeks, using a 64-slice CT scanner (Discovery CT750 HD GE Healthcare). Organ doses were also calculated. The MC code for dose distribution was validated through CT Dose Index (CTDI) measurements, following AAPM protocols. Volumetric CTDI values were normalized, developing an algorithm for fetal dose estimation across various body regions and exposure settings. Results: Fetal doses were within safe limits, indicating minimal risk to development. The study highlights the importance of minimizing radiation exposure, particularly through low-dose protocols. Additionally, optimizing CT parameters and using alternative imaging methods, such as ultrasound or MRI, are recommended when clinically feasible. Conclusions: This study presents a practical approach for estimating fetal radiation doses during CT scans, aiding in exposure reduction. Future research may expand this algorithm's validation across larger patient groups, emphasizing the need for radiology practices to employ the lowest dose possible and to consider non-ionizing imaging alternatives.

Keywords: *Monte Carlo Simulation, Fetal Radiation Dose, CT in Pregnancy, Low Dose Protocols*

ÖZ

Amaç: Travma veya klinik fayda gerektiren diğer durumlarda, gebe hastalarda bilgisayarlı tomografi (BT) taramaları gerektiğinde, fetüsün maruz kaldığı radyasyon dozunu doğru tahmin etmek önemlidir. Ancak mevcut yöntemler, rutin klinik kullanım için pratik değildir. Bu çalışma, Monte Carlo Simülasyon Yöntemi ile gebe hastalarda BT taramalarından kaynaklanan fetal ve organ dozlarını hesaplamayı amaçlamaktadır. Yöntemler: Farklı gebelik dönemleri (8-15 hafta) için gebe hasta fantomları kullanılarak 64 kesitli BT tarayıcı (Discovery CT750 HD GE Healthcare) ile Monte Carlo (MC) simülasyonları gerçekleştirildi. Organ dozları da hesaplandı. AAPM protokollerine göre BT Doz İndeksi (CTDI) ölçümleriyle doğrulanan MC kodu, hacimsel CTDI değerleri normalize edilerek fetal doz hesaplamalarında kullanılmak üzere bir algoritma geliştirildi. Bulgular: Fetüsün düşük radyasyon dozlarına maruz kaldığı ve bu seviyelerin fetal gelişim için risk oluşturmadığı gözlemlenmiştir. Çalışmada elde edilen dozlar, kabul edilebilir klinik sınırlar içerisindedir. Düşük doz protokollerinin kullanımı ve BT tarama parametrelerinin optimizasyonu, gebelikte radyasyon maruziyetini en aza indirmede etkilidir. Uygun olduğunda, ultrason veya MRI gibi iyonlaştırıcı olmayan alternatif görüntüleme yöntemleri önerilmektedir. Sonuçlar: Bu çalışma, BT taramaları sırasında fetal radyasyon dozlarını hesaplamak için uygulanabilir bir yaklaşım sunmaktadır. Geliştirilen algoritma, fetal maruziyeti azaltmada önemli bir araç olabilir. Gelecek çalışmalar, algoritmayı daha geniş hasta gruplarında doğrulayarak araştırmayı genişletebilir ve düşük doz protokollerinin önemini vurgulamaktadır.

Anahtar Kelimeler: *Monte Carlo Simülasyonu, Fetal Radyasyon Dozu, Gebelikte BT, Düşük Doz Protokolleri*

INTRODUCTION

Computed tomography (CT) is an established imaging modality in modern medicine that delivers rapid and high-resolution images for diagnostic and therapeutic purposes. The use of CT imaging has significantly increased over the past few years, particularly in certain populations like pregnant women, due to trauma injuries, cancer screenings, and other clinical applications (1). Because CT provides fast and accurate diagnostic information, it is often preferred in emergency situations, even for pregnant patients. However, the ionizing radiation involved poses risks, especially to radiosensitive tissues like the fetus (2).

The biological effects of ionizing radiation, such as DNA damage and cell death, are well-known and linked to cancer development (9). The developing fetus, especially during rapid cell division, is highly sensitive to radiation, leading to risks like developmental abnormalities, organ malformations, and a higher risk of cancer later in life (3). Thus, it's crucial to carefully assess radiation risks for both the mother and fetus during CT scans (4). Ideally, alternative imaging methods without radiation exposure, like ultrasound or MRI, should be used whenever possible. But in emergencies, where CT is necessary, the diagnostic method with the lowest possible radiation dose for both the mother and fetus should be selected (5).

The fetus's susceptibility to radiation depends on factors such as gestational age, patient anatomy, the distance between the uterus and the scanned region, and CT scan parameters (4). For instance, fetal doses from scans of the mother's neck or head are negligible, while direct scans involving the uterus may result in doses up to 50 mGy (6), which can significantly affect development.

Existing methods to estimate fetal radiation exposure during CT have practical limitations in clinical practice, often lacking accuracy or feasibility across different scenarios. Thus, there's a need for more reliable and clinically applicable models that can be easily integrated into workflows. Since radiation impacts rapidly dividing cells, such as those in a developing fetus, accurate fetal dose estimation during CT is critical to assess these risks. However, direct measurement is technically and ethically challenging (6), necessitating dependable models (7).

One of the most reliable ways to assess fetal radiation exposure is through Monte Carlo simulations. These simulate the interaction of photons and ionizing radiation with body tissues to provide accurate radiation absorption estimates (8). This method is widely used in pregnant patients through patient-specific models and phantoms. For example, Angel et al. (6) employed Monte Carlo simulations to estimate fetal doses at different gestational stages. These methods offer reliable dose estimations, yet further refinement is needed to integrate these results into real-time clinical decisions.

In conclusion, minimizing radiation risks for pregnant patients undergoing CT scans requires reliable dose estimation methods. Monte Carlo simulations and other modern techniques play a crucial role in this context (8). This study aims to calculate fetal radiation doses accurately using the NCICT simulation tool and emphasizes the clinical applicability of Monte Carlo methods. Additionally, it seeks to address the limitations of current fetal dose estimation practices by providing healthcare professionals with a validated tool.

MATERIAL and METHOD

This study employed the NCICT dosimetric simulation tool, which leverages a Monte Carlo-based approach, to precisely estimate organ doses in pregnant patients and fetuses undergoing CT scans (8). The NCICT system is specifically designed to simulate radiation exposure across various organs and calculate effective doses during CT imaging, providing detailed information critical for dose management in clinical settings (6). In this study, the tool was optimized to enhance its accuracy and applicability in assessing organ doses specific to pregnant patients and their fetuses (4).

Patient-specific data was incorporated to allow for realistic dose assessments in both pregnant individuals and their fetuses (5). Anthropomorphic models were selected to represent pregnancy stages between 8 and 15 weeks, capturing the natural anatomical changes occurring during early gestation. These models were sourced from the comprehensive NCICT database, ensuring that the simulations closely aligned with real clinical scenarios and reflected the unique anatomical characteristics of pregnant patients at each gestational age (3,8). The models were further adapted for use with the NCICT system, including adjustments to better represent pregnancy-specific anatomy, thus enhancing the fidelity and relevance of the simulation outcomes (6).

Simulation process, Monte Carlo simulations integrated within the NCICT framework enabled in-depth radiation dose calculations at the organ level. This method involves tracking the interactions of photon particles as they pass through different tissues, which is essential for accurately estimating energy deposition in radiosensitive areas such as the uterus and fetal organs. By incorporating a Python-based backend, the simulations were streamlined for efficient processing, which facilitated scalability and allowed for multiple patient models and CT scan protocols to be simulated with precision (6).

Detailed Steps for Dose Calculation: CT Scan Parameters Input: A Python-based interface was developed to input essential CT scan parameters, including tube voltage (kVp), tube current (mAs), scan length, pitch, rotation time, and scan mode (e.g., spiral or helical). These parameters were chosen based on clinical protocols typically used in diagnostic CT imaging for pregnant patients, ensuring that the simulations could replicate real-world clinical scenarios accurately (6). The choice of these parameters is critical, as variations can influence radiation dose and distribution, especially in sensitive anatomical areas.

Selection of Patient Models: Anthropomorphic models tailored for various gestational stages (8-15 weeks) were selected from the NCICT database. Each model represents specific anatomical characteristics associated with the given gestational period, reflecting changes in maternal and fetal anatomy. Python-based functions automated the model selection process, ensuring that the appropriate model was applied based on the patient's gestational age, allowing for an accurate assessment of radiation exposure relative to gestational development (8).

Monte Carlo Photon Simulations: In these simulations, photon interactions with tissues were simulated in detail, with each organ assigned specific absorption coefficients to determine the likelihood of photon interaction and energy transfer. The simulations were designed to focus on energy deposition within radiosensitive organs, such as the uterus, fetal brain, liver, and other critical organs, ensuring that radiation exposure estimates were as accurate as possible. Monte Carlo techniques accounted for variations in tissue composition, organ density, and anatomical location, providing a realistic representation of radiation distribution within the body (4).

Calculation of Organ Doses: Energy absorbed in each organ was converted into radiation doses, expressed in milligrays (mGy). This conversion involved calculating the absorbed dose for each organ based on the number of photon interactions, the energy deposited, and the organ's size and density. The results were then evaluated according to national and international radiation safety standards, specifically those outlined by the International Commission on Radiological Protection (ICRP) and the American Association of Physicists in Medicine (AAPM). These standards provided reference values to ensure that radiation exposure remained within clinically safe limits, particularly for vulnerable fetal tissues (9).

Validation of the Monte Carlo simulation results was conducted by comparing calculated doses with CT Dose Index (CTDI) measurements obtained in accordance with AAPM protocols (9). CTDI values serve as a standard metric for assessing radiation output from CT scanners, and aligning the simulation data with these values ensures consistency with clinical dosimetric

benchmarks. Additionally, comparisons were made with established dosimetric data from the literature, verifying the accuracy and reliability of the calculated doses. This validation process confirmed that simulated doses fell within acceptable error margins, underscoring the robustness of the Monte Carlo method in providing reliable estimates of fetal and maternal radiation exposure during CT scans (6).

Validation is crucial as it ensures the fidelity of the simulation tool, allowing healthcare professionals to confidently use these estimates in clinical decision-making.

Table 1: Summary of the CT Protocol Parameters

Parameter/Process	**Discovery CT750 HD - Brain Scan**	**Discovery CT750 HD - Thorax Scan**
Scan Type	Brain	Thorax
Rotation Time (s)	0.5	0.4
Detector Configuration (mm)	20	40
Table Speed (mm/rotation)	10.62	55
Tube Current (mA)	200	200
Tube Voltage (kVp)	100-120	100-120
Automatic Exposure Control (AEC)	Off	Off
Scan Field of View (SFOV)	Brain	Thorax
Reconstruction Algorithm	Standard	Standard
CTDIvol (mGy)	38.43	15
	Description/Components	
Input	CT Scan Parameters Entry	-kVp (tube voltage) -mAs (tube current) -Scan length -Pitch -Rotation time -Scan mode (spiral/helical)
Model Selection	Anthropomorphic Model Selection	-Gestational age (8-15 weeks) -Maternal anatomy models -Fetal anatomy models -Organ-specific parameters
Simulation	Monte Carlo Photon Simulation	-Tissue-specific absorption coefficients -Energy transfer calculations -Radiosensitive organ focus -Anatomical variation accounting
Calculation	Organ Dose Calculation	-Energy absorption quantification -Dose conversion to mGy -Organ-specific dose estimation -ICRP/AAPM standard comparison
Validation	Results Validation	-CT Dose Index (CTDI) measurements -Literature data comparison -Error margin assessment -Clinical benchmark alignment
Output	Results Visualization and Reporting	-Organ dose tables -Visual dose distribution maps -Fetal dose estimation -Clinical recommendation support

RESULTS

This study examined the organ doses for a pregnant woman during head CT scans performed at 8 and 15 weeks of gestation using Monte Carlo simulations. The results indicated comparable radiation doses between both gestational weeks, with slightly higher radiation absorption at 120 kVp compared to 100 kVp. The specific organ doses and their clinical relevance are discussed below.

Brain: While the brain is relatively resistant to radiation, the doses observed in this study (ranging from 37.67 mGy to 40.92 mGy) should be carefully considered, especially in pregnant patients. There are no immediate short-term effects linked to these doses, but long-term cumulative exposure may elevate neurological risks. CT scans during pregnancy are particularly important for fetal neurological development. The higher doses at 120 kVp, compared to 100 kVp, show that more radiation is absorbed at higher tube voltages.

Pituitary Gland: This critical endocrine organ, responsible for hormone production, was exposed to doses between 32 mGy and 36 mGy. These levels are of clinical concern, as radiation exposure to the pituitary during pregnancy could disrupt maternal hormonal balance, potentially affecting fetal development. Hormonal changes caused by radiation may have long-lasting effects on pregnancy outcomes.

Lens: The eye lens is highly sensitive to radiation, with doses in this study ranging from 45 mGy to 46 mGy. These levels are known to increase the risk of cataract formation, a condition resulting from cumulative radiation exposure. Therefore, such radiation levels should be monitored closely, particularly due to the cumulative nature of lens damage.

Eyeballs: Radiation exposure to the eyeballs was recorded at 44–45 mGy, approaching the threshold for eye health. While immediate risks are minimal, the long-term effects on sensitive eye tissues must be taken into account.

Salivary Glands: The salivary glands received relatively high doses (46–48 mGy), and prolonged exposure could lead to reduced saliva production, dry mouth, and potential loss of function. Monitoring radiation exposure to these glands is vital to prevent long-term damage.

Oral Cavity: Radiation doses to the oral cavity ranged from 36 to 39 mGy, posing a moderate risk to mucosal tissues. These doses may result in symptoms like mucosal damage and dry mouth, necessitating close monitoring in clinical settings.

Spinal Cord: Although significant radiation to the spinal cord can result in neurological issues, the doses observed in this study were low (4.45–4.91 mGy), and are unlikely to cause clinical effects. However, low-dose protocols should be maintained to minimize any potential risk.

Thyroid Gland: The thyroid, one of the most radiation-sensitive organs, was exposed to doses between 3.67 mGy and 3.98 mGy. Even low doses can increase the risk of thyroid cancer, so radiation to this area should be minimized whenever possible. Protective measures like thyroid shielding are recommended.

Other Organs (Esophagus, Trachea, Thymus, Lungs, Breast, Heart Wall): These organs were exposed to relatively low doses (0.7 to 10 mGy). While these doses are within acceptable limits for less sensitive organs, their long-term impact on critical organs, like the heart and lungs, should not be overlooked, especially in cases of repeated exposure.

Effective Dose: The effective dose, used to assess the overall impact of radiation exposure on health, ranged from 1.8 mSv to 1.95 mSv in this study. These values fall within acceptable limits for a CT scan. However, cumulative exposure to radiation over time still poses risks such as cancer.

Therefore, keeping radiation doses "As Low As Reasonably Achievable" (ALARA) is critical. Although the differences between 100 kVp and 120 kVp were minimal, slightly higher doses were observed at 120 kVp. This indicates that higher tube voltages lead to greater radiation absorption in organs. Radiation doses to sensitive organs like the eyes, thyroid, and salivary glands reached clinically significant levels, which requires careful consideration in clinical protocols. Although effective doses were within safety limits, the potential long-term effects on the fetus, especially concerning cumulative exposure, should not be ignored. Whenever possible, lower-dose protocols or alternative imaging methods, like MRI or ultrasound, should be preferred.

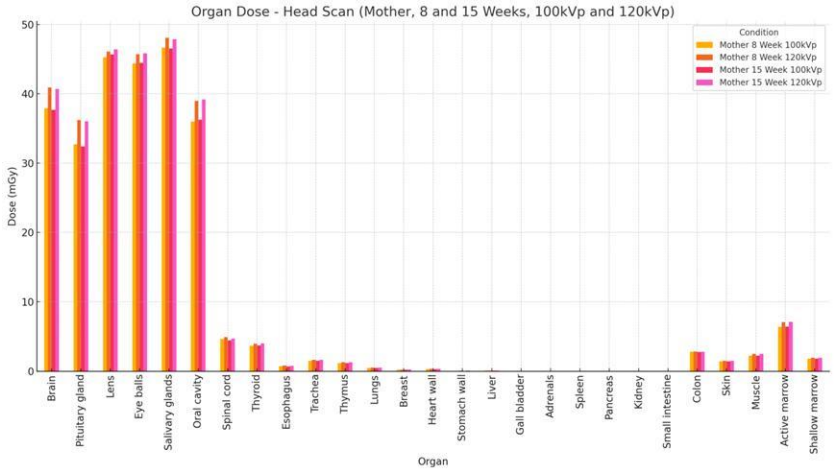

Figure 1: Mother Gestational Age (8-15 Weeks) Phantom with Different kVp Organ

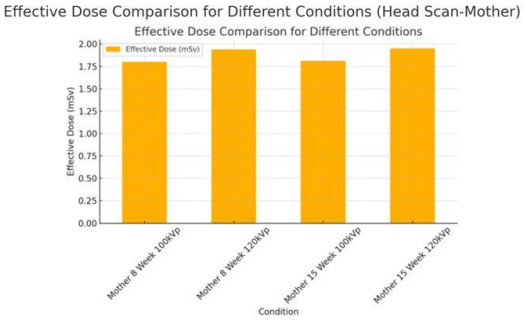

Figure 2: Mother Gestational Age (8-15 Weeks) Phantom with Different kVp Effective Doses Organ

The fetal organ doses for head CT scans at 8 and 15 weeks of gestation. The results indicate that no significant radiation exposure was observed in critical fetal organs such as the brain, pituitary gland, eye lenses, and eyeballs. This is a positive outcome, as it shows that these radiation-sensitive organs were effectively protected during the scans. The absence of radiation exposure to the brain and eye lenses is crucial for the fetus's long-term neurological and visual development.
At 8 weeks of gestation, the salivary glands and oral cavity received minimal radiation doses (0.01 mGy). These doses are extremely low and pose no clinical risk. At 15 weeks, no radiation was detected in these organs, reinforcing the conclusion that the overall exposure to the fetus was negligible.

For the spinal cord, doses ranged between 0.01 and 0.02 mGy. While the spinal cord is a vital structure, these radiation levels are so low that they are unlikely to cause any significant effects, such as nerve damage. The low radiation doses observed suggest that the developing nervous system was well protected.

The thyroid gland, known for its sensitivity to radiation, received doses ranging from 0.01 to 0.05 mGy. While radiation exposure to the thyroid carries the risk of thyroid cancer, the extremely low doses recorded in this study are considered low-risk and are unlikely to affect thyroid health adversely. The lack of radiation exposure to the thyroid early in pregnancy is a favorable outcome, reducing the risk of long-term complications.

Minimal radiation was also observed in internal organs such as the stomach and liver. At 8 weeks, the stomach received 0.06 mGy, while the liver received 0.01 mGy. No measurable radiation was detected in either organ at 15 weeks. These low doses are unlikely to have any significant impact on fetal organ development.

The digestive system, including the small intestine and colon, received approximately 0.02 mGy of radiation at 8 weeks. These low levels are generally considered safe and are unlikely to cause clinical concerns. Bone marrow, another radiation-sensitive tissue, received very low doses, with both active and shallow bone marrow exposed to 0.01 mGy at 8 weeks, posing minimal risk for conditions like bone marrow cancer or hematologic disorders.

The effective dose was also maintained at low levels, with an observed effective dose of 0.01 mSv. This is generally categorized as low risk, especially in the first trimester when critical neurological and physiological development occurs. These low radiation doses are considered safe, and the results suggest that the fetus was exposed to minimal radiation during the scans.

Organs such as the thyroid, spinal cord, digestive system, and bone marrow received doses ranging from 0.01 to 0.05 mGy. Although these doses do not pose significant clinical risk, it is essential to monitor every dose applied to developing fetal tissues. Overall, the radiation doses during these head CT scans were extremely low, with minimal risk of long-term effects on fetal development. However, due to the fetus's heightened sensitivity to radiation in early development, the use of low-dose protocols is strongly recommended. The effective dose of 0.01 mSv suggests low radiation exposure, with no significant impact on development expected. Nevertheless, alternative imaging modalities such as MRI or ultrasound should be considered whenever possible to further reduce radiation exposure.

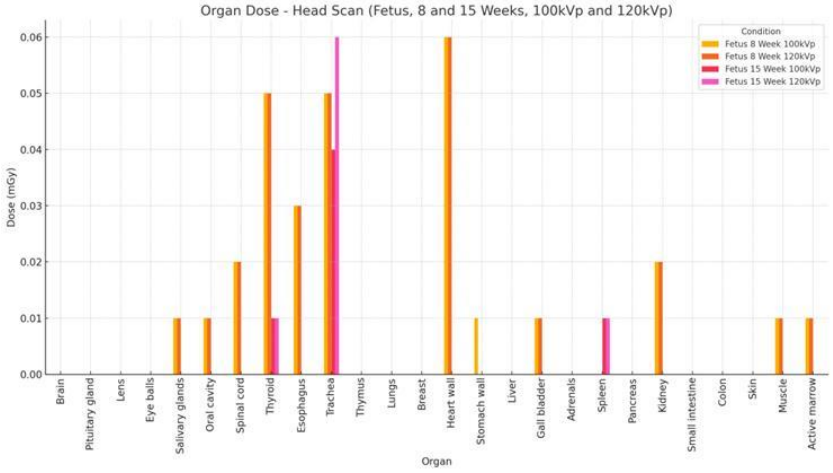

Figure 3: Fetus (8-15 Weeks) Phantom with Different kVp Organ Doses

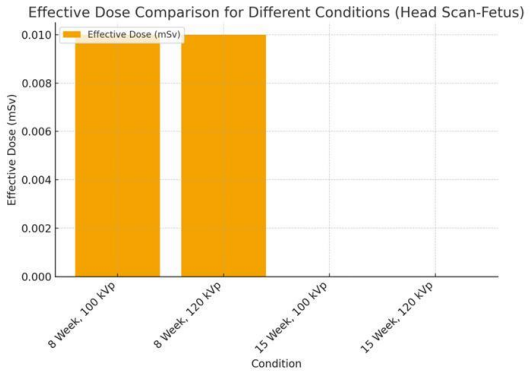

Figure 4: Fetus (8-15 Weeks) Phantom with Different kVp Effective Doses

The thoracic CT scan results performed at 8 and 15 weeks of gestation show varying radiation doses across different organs, emphasizing the importance of minimizing exposure, especially in radiation-sensitive organs.

Brain: The brain received relatively low doses during thoracic scans, ranging from 0.17 mGy to 0.2 mGy. While the brain is sensitive to radiation, these doses are low and pose no immediate clinical risk. However, the potential for cumulative radiation exposure and long-term neurological effects should not be overlooked, especially in individuals undergoing multiple scans.

Pituitary Gland: The pituitary gland, responsible for hormonal regulation, received doses between 0.19 mGy and 0.23 mGy. Though these levels are low, the gland's role in maintaining hormonal balance during pregnancy warrants careful monitoring. Even low doses could potentially impact long-term hormonal regulation, although no immediate harm is expected.

Eye Lenses and Eyeballs: The radiation doses observed for the eye lenses and eyeballs, ranging from 0.13 mGy to 0.17 mGy, are also low. The eye lens is highly sensitive to radiation, and while the risk of cataracts at these levels is minimal, the cumulative effects of repeated exposure should be considered. Currently, these doses are unlikely to cause significant clinical effects.

Salivary Glands: The salivary glands received higher radiation doses compared to other organs, with doses ranging from 1.34 mGy to 1.43 mGy. Long-term effects like salivary gland dysfunction or dry mouth may occur with repeated exposure. However, these doses are tolerable for single exams, although future scans should aim to reduce exposure to these glands.

Spinal Cord: The spinal cord received doses ranging from 6.31 mGy to 6.94 mGy. While these doses are not immediately harmful, the risk of nerve damage and neurological complications increases with cumulative exposure. Lower-dose protocols should be prioritized when scanning areas that expose the spinal cord, especially in pregnant patients.

Thyroid: The thyroid, highly sensitive to radiation, received significant doses of 17.22 mGy to 17.56 mGy. These levels could increase the long-term risk of thyroid cancer due to the thyroid's high radiation sensitivity. Shielding or minimizing exposure to the thyroid is highly recommended.

Esophagus and Trachea: These organs received radiation doses between 9.46 mGy and 11.00 mGy. While these doses are within acceptable limits, they may slightly increase the long-term risk of esophageal cancer. Immediate risks remain low, but cumulative exposure could have implications.

Lungs: The lungs, critical in radiation exposure, received doses ranging from 10.52 mGy to 11.27 mGy. This may increase the long-term risk of lung cancer, particularly with repeated exposure.

Reducing radiation to the lungs should be prioritized, especially for patients with pre-existing conditions or other risk factors like smoking.

Heart and Liver: The heart wall and liver received doses ranging from 8.89 mGy to 11.06 mGy. These organs could face long-term risks from cumulative radiation exposure, particularly for patients with pre-existing conditions. Repeated exposure to these doses may worsen underlying health issues.

Effective Dose: The overall effective dose ranged from 6.07 mSv to 6.48 mSv. While within acceptable limits for medical imaging, it is important to consider that the scan was performed on a pregnant patient. Lower-dose protocols should be used to minimize risks to the fetus.

Organ Doses: Radiation-sensitive organs like the thyroid, spinal cord, and lungs received moderate to high doses, especially at 120 kVp. The thyroid, in particular, is at higher risk due to its radiation sensitivity. Protective measures should be considered for future scans.

Fetal Risks: Although the thoracic scan was performed on the mother, minimizing fetal radiation exposure is essential. The effective doses fall within safe limits, but radiation exposure should always be minimized during pregnancy. Shielding and low-dose protocols are critical to protect both mother and fetus.

Comparison of Tube Voltages: Scans using 120 kVp resulted in higher radiation doses compared to 100 kVp. Whenever possible, lower-voltage scans (100 kVp) should be preferred to reduce radiation exposure without compromising diagnostic quality.

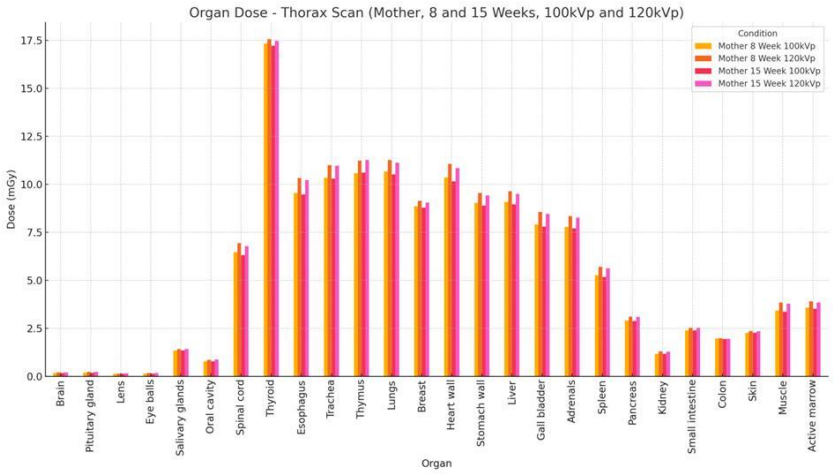

Figure 5: Mother Gestational Age (8-15 Weeks) Phantom with Different kVp Organ Doses

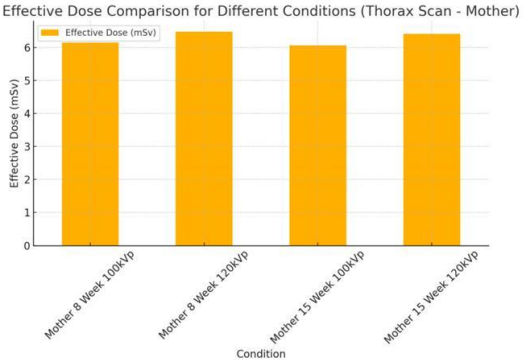

Figure 6: Mother Gestational Age (8-15 Weeks) Phantom with Different kVp Effective Doses

The fetal thoracic CT scan results at 8 and 15 weeks of gestation show minimal radiation exposure across most organs. Below is a detailed analysis of organ-specific radiation doses and their potential clinical impact on fetal development.

Brain and Pituitary Gland: At 8 weeks, no radiation exposure was detected in the brain and pituitary gland. However, at 15 weeks, these organs received doses between 0.05 mGy and 0.06 mGy. While these doses are low and unlikely to significantly affect fetal brain development, both the brain and the pituitary gland are highly sensitive to radiation. Therefore, even low-level exposure should be closely monitored to mitigate any potential risks to neurological development.

Eye Lenses and Eyeballs: No radiation was detected in the eye lenses and eyeballs at 8 weeks, but very low doses were recorded at 15 weeks (0.06–0.07 mGy). These doses pose minimal risk to eye health and are unlikely to cause cataracts. However, since fetal eye tissues are highly sensitive to radiation, continued monitoring is recommended to ensure no long-term adverse effects occur.

Salivary Glands and Oral Cavity: At 15 weeks, the salivary glands and oral cavity received low doses of radiation (0.04–0.05 mGy). While these doses are low and pose no significant risk to fetal development, the long-term effects on tissue development should be carefully evaluated, particularly with repeated exposure.

Spinal Cord: The spinal cord, crucial for fetal development, was exposed to doses between 0.04 and 0.06 mGy at 15 weeks. Although these levels do not pose substantial risks to spinal cord development, careful monitoring is recommended to protect this essential structure during critical periods of fetal growth.

Thyroid: The fetal thyroid, highly sensitive to radiation, received low doses (0.01 mGy at 8 weeks and 0.04–0.06 mGy at 15 weeks). While these doses are low and pose minimal risk, limiting radiation exposure to the thyroid is crucial. Monitoring and, where possible, shielding are advised to minimize exposure.

Lungs, Heart, and Chest Region: The fetal lungs, heart wall, and chest region were exposed to low doses (0.05–0.06 mGy) at 15 weeks. While these doses are low-risk for fetal development, the long-term effects on lung and cardiac function should be carefully monitored, especially given cumulative exposure.

Internal Organs (Stomach, Liver, Gallbladder, Kidneys): At 8 weeks, no radiation was detected in most internal organs, while at 15 weeks, doses ranged from 0.05 mGy to 0.09 mGy. These doses are low and generally pose no significant risks to fetal development. However, the long-term effects on organ growth and function should be considered, particularly with repeated imaging.

Digestive System (Small Intestine, Rectosigmoid Region): Radiation exposure to the small intestine and rectosigmoid region at 15 weeks ranged from 0.07 to 0.1 mGy. These doses are unlikely to impact fetal digestive system development, but minimizing exposure is recommended to reduce potential long-term risks.

Urinary and Reproductive Systems (Prostate, Testes, Ovaries): At 15 weeks, the bladder, prostate, testes, and ovaries were exposed to low doses (0.05–0.1 mGy). These doses are not expected to impact fetal reproductive system development significantly. However, since these organs are sensitive to radiation, close monitoring and dose minimization are advised.

Bone Marrow: Bone marrow, crucial for hematopoietic system development, received doses between 0.1 mGy and 0.12 mGy at 15 weeks. While these levels pose minimal risks to bone marrow

development, any radiation exposure to such sensitive tissues should be approached cautiously. The cumulative effects on long-term hematologic health warrant attention.

Effective Dose: The effective dose to the fetus at 15 weeks ranged from 0.07 to 0.09 mSv. These levels are within safe limits for fetal development. However, minimizing radiation exposure is essential due to the fetus's high sensitivity during early development. Lower-dose imaging protocols and alternative modalities, such as MRI or ultrasound, should be considered whenever feasible to avoid unnecessary radiation.

Although the radiation doses observed across fetal organs during thoracic scans are minimal, continued monitoring is vital to ensure long-term development is not adversely affected. This is particularly true for sensitive organs such as the brain, thyroid, spinal cord, and bone marrow. For organs like the thyroid and reproductive system, reducing exposure with dose minimization strategies and considering alternative imaging methods is highly recommended. The effective dose at 15 weeks remains within safe limits, but ongoing efforts to reduce fetal radiation exposure should be a priority, especially when repeated imaging is necessary.

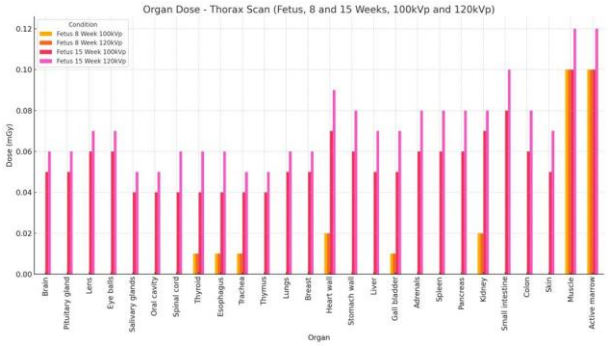

Figure 7: Fetus (8-15 Weeks) Phantom with Different kVp Organ Doses

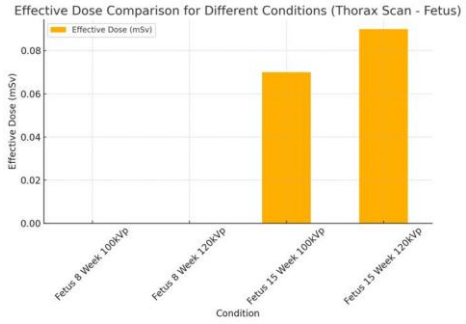

Figure 8: Fetus (8-15 Weeks) Phantom with Different kVp Effective Doses

DISCUSSION and CONCLUSION

This study used the NCICT dosimetric simulation tool, a Monte Carlo-based method, to estimate organ doses in pregnant individuals and fetuses from CT scans accurately (8,11). NCICT is a system that simulates radiation exposure to organs and calculates the effective dose during CT examinations (5). This tool was optimized in this study to improve performance in assessing organ doses for pregnant women and fetuses (4). The high-resolution simulation of radiation distribution within the body allows for precise dose estimation, crucial for reducing fetal exposure (2,10).

Patient-specific data were used to measure radiation doses in both pregnant patients and fetuses (5). Anthropomorphic models representing different stages of pregnancy (8 to 15 weeks) were utilized (3). Each model reflected the anatomical changes that occur during pregnancy and was

adapted for use with the NCICT system (6). These models were sourced from a comprehensive NCICT database, ensuring the accuracy and applicability of simulation outcomes in real clinical scenarios (8,11).

Organ dose calculations were performed using Monte Carlo simulations integrated into the NCICT system (7). The Monte Carlo method simulates radiation interactions with patient tissues in detail, enabling an accurate analysis of radiation deposition in specific organs (8). The simulations were integrated with the Python-based backend of the NCICT system for efficient processing, allowing scalability across multiple patient models and scan protocols (6,12).

For each CT examination (Table 1), patient-specific anatomical information and scan protocols were used to calculate organ doses. Custom Python scripts were created to optimize these calculations, ensuring the simulations were tailored to reflect individual patient characteristics, such as body size, organ positioning, and gestational stage—key factors for accurate dose estimation (3,13). The following steps were implemented:

1. CT Scan Parameters: A Python-based interface was developed to input CT scan parameters (kVp, mAs, scan length, spiral mode, etc.) for each patient. These parameters were selected based on clinical scan protocols typically used in pregnant patients undergoing diagnostic CT scans (6).
2. Selection of Patient Models: Anthropomorphic models for different gestational stages were used to simulate the anatomy of pregnant patients and fetuses. The model was selected from the NCICT database using a Python function, with each model tailored to accurately represent the anatomical changes at each gestational age (8).
3. Monte Carlo Simulations: Photon simulations were performed based on absorption coefficients assigned to each organ in the scanned region. Detailed calculations of energy transfer and radiation deposition were made, focusing on radiosensitive areas like the uterus and fetal organs (4,16).
4. Calculation of Organ Doses: Absorption values for each organ were converted into doses measured in milligrays (mGy). These doses were evaluated according to national and international radiation safety standards, including recommendations from the International Commission on Radiological Protection (ICRP) and the American Association of Physicists in Medicine (AAPM) (9,17).

Radiation dose calculations were performed using Monte Carlo simulation techniques integrated with the NCICT algorithm, following AAPM guidelines (9). The simulation results were validated against clinical CT Dose Index (CTDI) measurements (4). Additionally, comparisons with previously established dosimetric data in the literature further verified the accuracy of the calculated doses. This method is one of the most reliable for clinical dose assessment and is expected to guide future studies (8). Validation confirmed that simulated doses were within acceptable margins of error, demonstrating that the Monte Carlo method provides a robust framework for assessing fetal and maternal radiation exposure during CT scans (6). When CT scans are necessary during pregnancy, fetal protection measures should be implemented in addition to low-dose protocols. This recommendation may enhance the practical relevance of the study. These results highlight the importance of implementing low-dose protocols in clinical settings, which would strengthen the clinical impact of the study.

Future Applicability: This methodology can be applied in various clinical settings, allowing healthcare professionals to estimate radiation exposure more accurately and adjust CT scan protocols to minimize risk. As the NCICT system evolves, it could become a foundational tool for real-time dose optimization in clinical environments (8,19).

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Peripartum Depression and Contributing Factors: An Observational Study

Peripartum Depresyon ve Etki Eden Faktörler: Bir Gözlemsel Çalışma

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ÖZ

Amaç: Peripartum depresyon (PD) yaygın bir halk sağlığı sorunudur. Zamanında tanı ve tedavi çok önemlidir ve sağlık hizmeti sağlayıcılarının dikkatli bir şekilde ilgilenmesini gerektirir. Bu çalışma, Edinburgh Doğum Sonrası Depresyon Ölçeği'ni (EPDS) kullanarak peripartum depresyon riskiyle ilişkili demografik, klinik ve laboratuvar faktörlerini belirlemeyi amaçlamaktadır. Gereç ve Yöntem: Üniversite hastanemizin kadın doğum servis ve ayakta tedavi polikliniklerinden toplam iki yüz yirmi dokuz gebe ve doğum sonrası olgu, peripartum depresyon gelişme riskini ve katkıda bulunan faktörleri değerlendirmek için çalışmaya alındı. Demografik ve klinik özellikler, belirlenen laboratuvar değerleriyle (hemoglobin, tiroid hormonları ve D vitamini düzeyleri) birlikte analiz edildi. Bulgular: iki yüz yirmi dokuz olgu arasında (137 gebe, 92 doğum sonrası), %30,1'inin Edinburgh Doğum Sonrası Depresyon Ölçeği puanları anormal (13 ve üzeri) idi. İstatistiksel analiz, maternal obstetrik risk faktörlerinin, fetal ve neonatal sağlık sorunlarının ve düşük D vitamini düzeylerinin perinatal depresyon riskinin artmasıyla önemli ölçüde ilişkili olduğunu gösterdi. Sonuçlar: EPDS, yoğun kadın doğum servis ve polikliniklerinde peripartum depresyon riskini taramak için pratik bir araçtır. Obstetrik anne sağlık sorunları, fetal veya neonatal sağlık sorunları ve düşük D vitamini seviyeleri daha yüksek PD riskine katkıda bulunabilir. Bu risk faktörlerine sahip hamile veya lohusa kadınlar peripartum depresyonuna ilerlemesi açısından yakından izlenmeli ve endike olduğunda bir psikiyatri uzmanına yönlendirilmelidir.

Anahtar Kelimeler: *Perinatal depresyon, Doğum sonrası, Gebelik, Depresyon, D vitamini*

ABSTRACT

Objective: Peripartum depression (PD) is a common public health problem. Timely diagnosis and management are crucial and require careful attention from healthcare providers. This study aims to identify demographic, clinical, and laboratory factors associated with PD risk using the Edinburgh Postnatal Depression Scale (EPDS). Materials and Methods: A total of two hundred and twenty-nine pregnant and postpartum subjects were recruited from our university hospital's inpatient and outpatient clinics to evaluate peripartum depression development risk and contributing factors. Demographic and clinical characteristics, along with certain laboratory values (hemoglobin, thyroid hormones, and vitamin D levels) were analyzed. Results: Among the 229 subjects (137 pregnant, 92 postpartum), 30.1% had abnormal EPDS scores (≥13). Statistical analysis showed that maternal obstetric risk factors, fetal and neonatal health issues, and low vitamin D levels were significantly associated with an increased risk of perinatal depression. Conclusions: EPDS is a practical tool for screening PD risk in busy obstetrics inpatient and outpatient settings. Obstetric maternal health issues, fetal or neonatal health problems, and low vitamin D levels may contribute to a higher risk of PD. Pregnant or postpartum women with these risk factors should be closely monitored for PD progression and referred to a psychiatric professional when indicated.

Keywords: *Perinatal depression, Postnatal, Pregnancy, Depression, Vitamin D*

INTRODUCTION

Perinatal or peripartum depression (PD), formerly known as postnatal depression, is a significant healthcare concern. The prevalence of PD varies from 9% to almost 40%, depending on the region sampled (1-3). Limited studies in Turkey have reported prevalence rates ranging from 14% to 41% (4-8). As expected, demographic and economic factors as well as the population sampled (antepartum /postpartum, inpatient/outpatient settings) contribute to these variations.

The latest edition of the DSM-5, published by the American Psychiatry Association, includes a "peripartum onset" specifier for diagnosing peripartum depression, covering episodes that occur in pregnancy and within four weeks after delivery (9). The World Health Organization (WHO), in the “International Classification of Diseases – 10th Revision” (ICD-10), defines postpartum depression as episodes occurring within six weeks of delivery (10). Nevertheless, studies suggest that the prevalence of antepartum and postpartum onset is similar (11).

PD affects not only pregnant and postpartum patients but also the long-term health of their newborns, as an increasing number of studies suggest lingering effects. These effects can be psychological (e.g., anxiety, depression, and behavioral issues) as well as physical (e.g., an increased incidence of asthma, diabetes, and intestinal problems) (12-14). Screening for PD can be conducted using one of several available questionnaires. Edinburgh Postnatal Depression Scale (EPDS) is a practical tool that can be used in busy clinical settings to screen not only postpartum but also antenatal patients for PD risk (15,16). EPDS has been validated in Turkish (17). However, a definitive diagnosis of PD can only be made through face-to-face psychiatric evaluations.

The exact cause of PD remains unknown, but several factors including genetics, hormonal and nutrient imbalances, low socioeconomic status, pregnancy complications, and fetal or newborn health problems have been linked to its development. A prior history of depression is widely recognized as a major risk factor for PD (3,18).

The objective of this study was to assess the risk factors associated with the development of PD in both pregnant and postpartum individuals. Therefore, we conducted this study at our university hospital's outpatient and inpatient clinics to identify demographic, clinical, and laboratory factors related to the development of PD.

MATERIAL and METHOD

This was a prospective observational study conducted at Aydin Adnan Menderes University Hospital’s Obstetrics and Gynecology inpatient and outpatient clinics. The hospital is located in Aydin Province in Turkey with a population of 260,000. Ethical approval from the Institution’s Review Board has been obtained before the beginning of the study (Aydin Adnan Menderes University Ethical Board for Non-Invasive Clinical Research, Decision Number 12, Protocol Number 1024/152, and Date of 29/11/2024). The study was conducted by the principles of the "Helsinki Declaration".

The inclusion criteria required participants to be either pregnant or within the puerperium period (the first six weeks postpartum), have proficiency in speaking and understanding Turkish, and provide consent to participate. The exclusion criteria included the following: lack of consent to participate, a previous diagnosis of anxiety or psychiatric disorders, and inability to speak or understand the Turkish language.

Both antepartum and postpartum subjects were approached in the obstetrics and gynecology outpatient clinic. Several subjects were also recruited from inpatient labor and delivery services during their hospital stay for labor or pregnancy issues such as preterm labor or diabetes management. Subjects were asked a standard set of questions regarding their demographic and clinical information. The information form consisted of 24 questions about their age, marital status, gestational status, intended/unintended pregnancy, social support system, smoking status, systemic

disease history, prenatal care status (including obstetric complications, and fetal anomalies), mode of delivery, and the need for neonatal intensive care (NICU) after delivery. Adverse situations and pregnancy complications were later classified under "maternal factors" such as gestational diabetes, abruptio placenta, preterm premature membrane rupture, and oligo/polyhydramnios. Problems and complications regarding the fetus were named under "fetal factors" such as fetal anomaly on antenatal ultrasound, karyotype abnormality, and twin complications.

For PD risk assessment, the Edinburgh Postnatal Depression Scale (EPDS) was used. EPDS is a self-administered questionnaire used to screen both antepartum and postpartum women for PD risk. It consists of 10 multiple-choice questions regarding sleep, anxiety, sadness, and suicidal tendencies. Each choice equals 0 - 3 points (minimum 0, maximum 30 points). The total score is calculated at the end. The cut-off value for "high risk for depression status" is 13 points, although different cut-off points have been used resulting in different sensitivity and specificity levels (19, 20). EPDS has already been validated for use in Turkish (17).

Recent hemoglobin (Hgb), thyroid-stimulating hormone (TSH), and serum vitamin D levels were obtained from health records within one month of EPDS questionnaire administration to assess anemia, thyroid disease, and vitamin D deficiency, respectively.

Sample Size and Power

A sample size of at least 219 subjects was calculated to achieve 80% power with a 5% margin of error and 95% confidence interval. Following data collection, EPDS scores were examined for potential correlations with patient characteristics and clinical/laboratory data using NCSS 2020 software (NCSS LLC, Kaysville, Utah, USA). Descriptive statistics were presented, and data conformity to normal distribution was analyzed using the Shapiro-Wilk test. Student's t-test was used for normally distributed variables, one-way ANOVA test was used for three-group differences. The Mann-Whitney U and Kruskal-Wallis tests were used for variables that were not normally distributed. The effects of independent variables were analyzed by using regression models. Analyses were evaluated in 95% CI and $p<0.05$ level of significance.

RESULTS

A total of 229 subjects were recruited during the designated study period. Among these, 137 (59.8%) were pregnant and 92 (40.2%) were postpartum subjects (Table 1). The pregnant group was divided into early pregnancy (<28 weeks, n = 64) and late pregnancy (>28 weeks, n = 73) subgroups for further analysis. Descriptive statistics for demographic and clinical data were given in Table 1, such as gravida, parity, marital status, smoking, systemic disease, singleton/multifetal pregnancy, presence of support system, intended/unintended pregnancy, maternal obstetric factors (gestational diabetes, hypertension, etc.), presence of fetal factors (fetal anomalies, twin complications, etc.) and neonatal intensive care (NICU) admissions for postpartum subjects. Mean EPDS scores and laboratory values (hemoglobin, vitamin D, and TSH) were also provided in Table 1. No correlation was identified between EPDS scores and hemoglobin levels.

The mean age of the participants was 29.5±5.9 years for the whole group and 28.9±5.9 years for the pregnancy group. Mean age was slightly higher in the postpartum group than in the late pregnancy group (30.6±5.7 vs 28.8±5.7, respectively, $p = 0.04$).

Subjects with fetal factors were more common in the postpartum group than in early ($p = 0.03$) and late pregnancy groups ($p = 0.04$). Similarly, maternal factors were more common in the postpartum group than pregnancy groups ($p = 0.02$ for early and $p = 0.05$ for late pregnancy group). The postpartum group had lower vitamin D levels than the late-pregnancy group ($p = 0.05$).

Table 1: Demographic and Clinical Data of the Study Population

	Pregnant total(n=137)	Pregnant ≤28 (n=64)	Pregnant >28 (n=73)	Postpartum (n=92)	Total (n=229)
Age, years (mean±SD)	28.9(±5.9)	29.0(±6.1)	28.8(±5.7)	30.6 (± 5.7)	29.5±5.9
Marital status, married, n(%)	135(98.5%)	63(98.4)	72(98.6)	91(98.9)	226(98.6)
Smoking status, yes, n(%)	16(11.7)	9(14.1)	7(9.6)	12(13.0)	28(12.2)
Systemic disease yes, n(%)	53(38.7)	22(34.4)	31(42.5)	33(35.9)	86(37.5)
Pregnancy Related Variables					
Previous Pregnancies					
Nullipara, n (%)	71(51.8)	35(54.7)	26(35.6)	9(9.8)	80(34.9)
Previous CS, n (%)	43(31.4)	23(35.9)	21(28.8)	64(69.6)	107(46.7)
Previous VD, n (%)	24(17.5)	10(15.6)	14(19.2)	11(12.0)	35(15.3)
Previous CS and VD), n(%)	7 (5.1)	2 (3.1)	5 (6.8)	8 (8.7)	15 (6.6)
Intended pregnancy, yes n(%)	103(75.2)	49(76.7)	54(74.0)	63(68.5)	166(72.5)
Singleton, n(%)	128(93.4)	60(93.8)	68(93.2)	86(93.5)	214(93.4)
Multifetal, n(%)	9(6.6)	4(6.3)	5(6.9)	6(6.5)	15(6.6)
Gravida, IR/(Min-Max)	3-7 (1-9)	3-7 (1-8)	3-7 (1-9)	3-7(1-9)	3-7(1-9)
Parity, IR/(Min-Max)	1-3(0-5)	1-3(0-5)	1-3(0-3)	1-3(0-5)	1-3 (0-5)
Alive child, IR/(Min-Max)	1-3(0-5)	1-3 (0-5)	1-3 (0-3)	1-3 (0-5)	1-3 (0-5)
Fetal Factors*, yes n(%)	15 (6.9)	6 (9.4)	9 (12.3)	19 (20.6)	34 (14.8)
Maternal Factors** , yes n(%)	77 (57.7)	35 (54.7)	42 (57.5)	70 (76.1)	147 (64.2)
Newborn NICU admission- yes, n (%)				35 (38.1)	
Neonatal health problem -yes ***n (%)				70 (76.1)	
Postnatal social support system, yes, n (%)				88 (95.7)	
EPDS scores and Laboratory variables					Total
EPDS score, Average (Min-Max)	7.0(0-19.0)	7.6(0-19.0)	6.9(0-17.0)	8.0(0-22)	7.6(0-22)
Vitamin D level, ng/ml) Average, (Min-Max)	16.5(4.9-54.0)	17(5-37)	15.9(4.9-54)	15.8(2.7-43)	16.3(2.7-54)
Hgb level, (g/dl) Average, (Min-Max)	11.1(8.0-17.1)	11.3 (8.0-14.2)	10.9(8-17.1)	10.1(7.5-14.2)	10.9(7.5-17.1)
TFT- hypothyroidism, Yes n(%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

EPDS: Edinburgh Postnatal Depression Scale, CS: Cesarean section, VD: Vaginal delivery, SD: Standard deviation NICU: Neonatal Intensive Care Unit, TFT: Thyroid function tests, Hgb: hemoglobin, IR: Interquartile range, 25-75%. *Fetal Factors: intrauterine growth retardation (IUGR): 4 cases. Congenital pulmonary adenoid malformation: 1 case. IUGR and delX chromosome: 1 case, trisomy 21: 1 case, monochorionicity: 1 case. **Maternal Factors: GDMA1: Gestational diabetes A1, GDMA2: Gestational diabetes A2. IUGR, oligohydramnios, abruptio placenta, intrahepatic cholestasis, hydronephrosis, co-twin in-utero ex, preterm membrane rupture.***Neonatal health problems: neonatal tachypnea: 2 cases, hypoglycemia: 3 cases, jaundice: 1 case, prematurity: 14 cases, microcephaly and duodenal atresia: 1 case, tricuspid regurgitation and ventricular septal defect: 1 case, hypoglycemia and respiratory distress syndrome (RDS): 1 case, hydrocephalus: 1 case, ventricular septal defect: 1 case, prematurity and RDS: 1 case.

EPDS Scores (above vs under the cut-off value)
In the whole study population (229 subjects), 30.1% of patients had abnormal (at or above the cut-off value of 13) EPDS scores (Table 2). Subjects with abnormal EPDS scores had a lower mean gestational age (27.7 weeks vs 25.9 weeks, p = 0.02), but a higher percentage of fetal and maternal factors (p = 0.03 and p = 0.02) (Table 3). Also, vitamin D levels were found to be significantly lower in the abnormal EPDS score group (15.9±7.7 ng/ml, p = 0.02). There were no other statistically significant differences between normal and abnormal EPDS score groups (Table 3).

Table 2: EPDS Scores and Study Population

Category	Pregnant ≤28w (n=63)	Pregnant >28w (n=73)	Postpartum (n=93)	Total (n=229)
EPDS Score 1-12, n (%)	43 (68.3)	54 (74.0)	63 (67.7)	160 (69.9)
EPDS Score ≥13, n (%)	20 (31.7)	19 (26.0)	30 (32.3)	69 (30.1)

EPDS: Edinburgh Postnatal Depression Scale, w: weeks

Table 3: Comparison of Demographic/Clinic and Laboratory Characteristics by EPDS Cut-Off Value

Category	EPDS Score 0-12 (n=160)	EPDS Score ≥13 (n=69)	p value
Age, years, mean (±SD)	28.8±5.7	29.0±5.7	1.56
Marital status – married (%)	150(%)	51(%)	1.97
Smoker – Yes, n(%)	34(19.2)	12(23.1)	0.12
Gestational weeks, mean(±SD)	27.9±8.6	24.8±7.1	0.02
Intended pregnancy, Yes, n(%)	103(75.2)	63(68.5)	0.06
Singleton, yes n(%)	172(97)	49(93.5)	0.09
Fetal Factors, Yes, n(%)	22(13.0)	13(26.9)	0.03
Maternal Factors, Yes, n(%)	108(61.0)	40(76.9)	0.02
Laboratory findings			
Vitamin D level (ng/ml)	17.0±7.6	15.9±7.7	0.02
Hgb level (g/dl)	10.4±1.8	10.4±1.5	1.83

Student's t-test, Chi-square test. EPDS: Edinburgh Postnatal Depression Scale, SD: standard deviation, Hgb:Hemoglobin

Subgroups and EPDS Scores

In subgroup analysis, the abnormal EPDS score frequency was 31.7% in the early pregnancy group, 26% in the late pregnancy group, and 32.3% in the postpartum group (Table 2). Demographic variables were not different among groups based on normal and abnormal EPDS scores. EPDS scores were significantly higher in the postpartum group compared to the late-pregnancy group (p = 0.05). Also, vitamin D levels were significantly lower in the postpartum group than in the early pregnancy group (p = 0.05).

Table 4: Subgroup Demographic and Clinical Data Comparison

Parameter	Pregnancy ≤28w – Pregnancy >28w	Postpartum – Pregnancy ≤28w	Postpartum – Pregnancy >28w	Postpartum – Pregnancy
Demographic and clinical characteristics				
Age	p = 0.05	p = 0.14	p = 0.04	p = 0.03
Marital status, married	p = 0.15	p = 0.24	p = 0.17	p = 0.23
Smoker, yes	p = 0.13	p = 0.10	p = 0.02	p = 0.14
Systemic Disease	p = 0.25	p = 0.18	p = 0.30	p = 0.10
Obstetric characteristics				
Nulliparity	p = 1.92	p = 0.17	p = 1.12	p = 1.31
Previous CS	p = 1.36	p = 1.41	p = 1.37	p = 1.23
Previous VD	p = 0.67	p = 1.32	p = 0.54	p = 1.09
Previous CS and VD	p = 1.31	p = 1.85	p = 1.37	p = 1.52
Intended pregnancy	p = 0.14	p = 0.09	p = 0.08	p = 0.09
Singleton	p = 0.18	p = 0.09	p = 0.07	p = 0.09
Gravida	p = 0.12	p = 0.09	p = 0.08	p = 0.12
Parity	p = 0.06	p = 0.17	p = 0.11	p = 0.07
Alive children	p = 0.17	p = 0.12	p = 0.13	p = 0.12
EPDS Score and Laboratory Variables				
EPDS Score	p = 0.13	p = 0.21	p = 0.05	p = 0.22
Vitamin D level	p = 0.44	p = 0.05	p = 0.09	p = 0.18
Hemoglobin level	p = 0.25	p = 0.18	p = 0.08	p = 0.07

T-Test (Parametric), Mann-Whitney U Test (Non-parametric, two groups), Chi-square Test (categoric), Fisher's Exact Test, statistical significance level p<0.05. EPDS: Edinburgh Postnatal Depression Scale, CS: cesarean section, VD: vaginal delivery

Regression Analyses EPDS Scores (No Cut-off Value)

Association between EPDS scores and independent variables evaluated for their effect by multivariate regression analysis. Maternal and fetal factors were significantly related to EPDS scores (β= 2.40, p<0.00 and β= 3.5, p<0.00 respectively). Also, smoking and low vitamin D levels were significantly associated with higher EPDS scores (β= 0.92, p = 0.05 and β= -0.08, p = 0.05, respectively) (Supplementary Table 1).

Regression Analyses of EPDS Scores (by Cut-off Value)

When abnormal EPDS scores (above cut-off value) and other variables were investigated, a binary logistic regression analysis revealed that fetal factors (OR = 0.85, p = 0.04), maternal factors (OR = 2.40, p = 0.05), higher gravida (OR = 1.31, p = 0.03) and low vitamin D level (OR=0.98, p=0.05) were significantly associated with abnormal EPDS scores (Supplementary Table 2).

Correlation Analyses

EPDS scores and other variables were compared by using Pearson/Spearman correlation analysis. Fetal factor history had a strong positive correlation and vitamin D levels had a strong negative correlation with EPDS scores (without cut-off value) ($r=0.65$, $p<0.001$ and $r=-0.61$, $p<0.001$). Other variables with weak or no correlation to EPDS scores were also provided (Supplementary Table 3).

DISCUSSION

Peripartum Depression (PD) represents a critical healthcare issue impacting women of reproductive age as well as their newborns. The substantial physiological changes and hormonal fluctuations that occur during pregnancy and the puerperium phase elevate the risk of depression. Undiagnosed PD can lead to unfavorable outcomes. Women with PD are at risk for major depression, suicide, and harming their baby (21). Antenatal onset of depression may also have negative effects on fetal neural development (22).

Several risk factors for PD development have been proposed aside from hormonal changes. A prior depression diagnosis in the past is considered a major risk factor. Additional risk factors include young or advanced maternal age, low socioeconomic status, unintended pregnancy, multiparity, pregnancy complications, anemia, vitamin D deficiency, and maternal distress related to obstetric or newborn health issues (12, 23-25).

EPDS is widely used to screen both pregnant and postpartum women at risk for developing PD (15). Nevertheless, there are other alternatives such as Beck Depression Inventory, Patient Health Questionnaire 9, and Zung Self-Rating Depression Scale. All these screening approaches have sensitivity and specificity levels ranging between 50-100% (19,20,23). Increasing a test's sensitivity by asking more questions is possible but limiting the number of questions makes it practical for use in busy healthcare settings. EPDS is useful both in the antepartum and postnatal period for PD screening (16). However, it must be emphasized that the EPDS is used for screening purposes, not for final PD diagnosis. High scores should lead to a referral for psychiatric evaluation of the patient. In this study, we aimed to include both postpartum and pregnant subjects because PD symptoms can also be observed during pregnancy, and early intervention is important. The mean age of the pregnancy group was 28.9±5.9 years. No significant association was identified between abnormal EPDS scores and the mean age variable, despite some studies indicating that both younger and older ages could be associated with an increased risk of PD (26,27).

Some observations suggest that being married may reduce the risk of PD (28); however, in our study, 98.5% of participants were married, making it difficult to assess the relationship between depression risk and marital status.

In this study, a higher gravida number was identified as being associated with abnormal EPDS scores through logistic regression analysis ($OR=1.31$, $p = 0.03$, data not shown). Several pieces of evidence in the literature support the association between higher gravida numbers and an increased risk of postpartum depression (29).

Smoking during pregnancy is also suggested as a possible risk factor for PD (30). Our results revealed a weak positive correlation between smoking status and linear EPDS scores ($r=0.19$, $p = 0.05$, Supplementary Table 3). Systemic (chronic) disease history was not associated with increased PD risk in our study. However, previous research suggested an elevated PD risk in women with a history of systemic disease (31). It is possible that other factors may influence this potential risk factor. We could not interpret the variable thyroid hormone levels for PD risk due to an insufficient number of subjects with abnormal levels. Unintended pregnancies were pointed out as an additional stress factor for PD development (32). Our results showed no relationship between the intended/unintended pregnancy variable and abnormal EPDS scores. Likewise, no associations were

observed between multifetal pregnancy, singleton pregnancy, parity number, previous mode of delivery, hemoglobin levels, and abnormal EPDS scores.

Approximately thirty percent (30.1%) of the whole study population had abnormal EPDS scores. It was 28.6% in the pregnancy group and 32.3% in the postpartum group (Table 2). The observed frequencies align with previous findings, indicating that PD is not uncommon during the antenatal period. Therefore, it is essential that screening for postpartum depression (PD) is not limited solely to postpartum patients.

Maternal and fetal factors were significantly higher in the abnormal EPDS score group (Table 1). It can be inferred that fetal and maternal factors can be a source of significant distress. These may include any diagnoses or findings related to pregnancy, such as gestational diabetes, preterm labor, placental issues, amniotic fluid volume abnormalities, complications specific to twin pregnancies, fetal growth restriction, and fetal anomalies. Many studies in the literature have reported maternal and/or fetal issues that elevate the risk of PD (33). Hence, patients with maternal obstetric problems and/or fetal issues may warrant screening for PD.

In this study, serum vitamin D levels were significantly lower in the group with abnormal EPDS scores. A strong negative correlation was observed between serum vitamin D levels and EPDS scores ($r=-0.61$, $p<0.001$, Supplementary Table 3). Vitamin D is a molecule with immunomodulator and anti-inflammatory properties. Recent studies indicate that low vitamin D levels during pregnancy and postnatal periods may be linked to PD, though the exact mechanism remains unknown (34). However, whether vitamin D supplementation would improve the EPDS scores is not clear (35). Although controversial, vitamin D level measurement during pregnancy and supplementing the subjects with low levels may be warranted.

Limitations

The study's limitations included omitting socioeconomic statuses, a low number of postpartum subjects, and heterogeneity of the groups in terms of inpatient/outpatient recruitment. The strengths of this study included power size calculation, a relatively low migrant population in the area (homogeneous population), and coverage of both prenatal and postnatal subjects while investigating vitamin D levels. Future research should explore whether interventions such as vitamin D supplementation or targeted support for women facing obstetric complications can effectively reduce PD risk.

CONCLUSION

Our study found that higher gravida numbers, the presence of maternal and fetal factors, and low serum vitamin D levels were significantly associated with elevated EPDS scores. Although other factors such as systemic disease history and thyroid hormone levels were examined, only the aforementioned variables demonstrated statistically significant correlations with PD risk.

This prospective observational study indicates that low vitamin D levels, the presence of obstetric or fetal health issues, and high parity are significantly associated with an increased risk of peripartum depression, as reflected by elevated EPDS scores. These findings underscore the importance of implementing routine PD screening for both pregnant and postpartum women, particularly among those with identified risk factors.

Ethical Approval: Ethical approval from the Institution's Review Board has been obtained prior to the beginning of the study (Aydin Adnan Menderes University Ethical Board for Non-Invasive Clinical Research, Decision number 12, Protocol number 1024/152, and date of 29/11/2024). The study was conducted in line with the principles of the "Helsinki Declaration". Written informed consent to participate and publish was obtained from all individual participants or legal guardians included in the study.

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

Authors Contributions: EZ: Conceptualization, data curation, formal analysis, project administration, investigation, methodology, validation, writing-original draft.
TYO: Formal analysis, investigation, methodology, resources, supervision, validation, writing-review & editing.
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Depression, Anxiety, Stress, and Associated Factors among Pharmacy Students Following the COVID-19 Pandemic

COVID-19 Salgını Sonrası Eczacılık Öğrencilerinde Depresyon, Kaygı, Stres ve İlişkili Faktörler

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ABSTRACT

COVID-19, which initially originated in the city of Wuhan, China at the end of 2019, caused millions of cases and deaths worldwide. Considering the conditions that arose during the pandemic, the psychological well-being of the students was affected by many factors related to COVID-19. This study has aimed to investigate the prevalence of depression, anxiety, and stress related to the COVID-19 and possible factors affecting depression, anxiety, and stress among pharmacy students. The mental health status of participants was examined using the Depression, Anxiety, and Stress Scale (DASS-21). Association analysis using non-parametric tests was performed for categorical, ordered, and dichotomous predictors. Logistic regression analysis was applied to investigate the effects of explanatory variables on the mental health of the students. Based on the findings, the prevalence of severe/extremely severe depression, anxiety, and stress were found to be 16.6%, 28.2%, and 12.0%, respectively. We also found significant effects of investigated factors, e.g., having a psychiatric disease, relationship with the family or friends, having anyone in the family who lost his/her job during the pandemic, having a need for psychiatric support, having anyone in the family diagnosed with COVID-19, on the depression, anxiety, and stress levels of the students. Our findings showed that the factors related to COVID-19 might have led to an increase in depression, anxiety, and stress levels among the students. These parameters must be taken into consideration both for the protection of students' psychological well-being and for the guidance of their education and training activities.

Keywords: *COVID-19, Mental health, Pharmacy students, Logit regression model*

ÖZ

İlk olarak 2019 yılı sonunda Çin'in Wuhan şehrinde ortaya çıkan COVID-19, dünya çapında milyonlarca vakaya ve ölüme neden oldu. Pandemi sürecinde ortaya çıkan koşullar göz önüne alındığında öğrencilerin psikolojik iyilik hallerinin Covid-19 ile ilgili birçok faktörden etkilendiği görülmüştür. Bu çalışma, eczacılık öğrencileri arasında COVID-19'a bağlı depresyon, anksiyete ve stresin yaygınlığını ve depresyon, anksiyete ve stresi etkileyen olası faktörleri araştırmayı amaçlamıştır. Katılımcıların ruh sağlığı durumları Depresyon, Kaygı ve Stres Ölçeği (DASS-21) kullanılarak incelendi. Kategorik, sıralı ve ikili değişkenler arasındaki anlamlılık ilişkisi parametrik olmayan testler kullanılarak analiz edişmiştir. Açıklayıcı değişkenlerin öğrencilerin ruh sağlığı üzerindeki etkilerini araştırmak amacıyla lojistik regresyon analizi uygulanmıştır. Bulgulara göre şiddetli/aşırı şiddetli depresyon, anksiyete ve stres yaygınlıkları sırasıyla %16,6, %28,2 ve %12,0 olarak bulunmuştur. Psikiyatrik bir hastalığın olması, aile veya arkadaşlarla ilişki, ailede pandemi sırasında işini kaybeden birinin olması, psikiyatrik desteğe ihtiyaç duyulması, ailede herhangi birinin salgın sırasında işini kaybetmesi gibi faktörler ile anlamlı ilişki bulunmuştur. Bulgularımız, COVID-19 ile ilgili faktörlerin öğrencilerde depresyon, kaygı ve stres düzeylerinde artışa yol açmış olabileceğini göstermiştir. Hem öğrencilerin psikolojik iyiliklerinin korunması hem de eğitim-öğretim faaliyetlerinin yönlendirilmesi açısından bu parametrelerin dikkate alınması gerekmektedir

Anahtar Kelimeler: *COVID-19, Ruh sağlığı, Eczacılık öğrencileri, Logit regresyon modeli*

INTRODUCTION

By the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which had its origins in Wuhan, China had spread over the world and resulted in millions of cases and deaths. People have witnessed substantial changes in many fields, including health, socio-economic, education, and social life, as a result of the global pandemic caused by the COVID-19 virus (1). Besides, given the conditions that arose during the pandemic, many factors related to COVID-19 had an impact on psychological well-being globally (2). College students were more susceptible to mental health problems due to pandemic-related stressors and constraints, which could have an adverse effect on their educational performance and social relationships (3).

Unexpected changes in conditions have a negative effect on human psychology, which is an unavoidable reality (4). According to the World Health Organization, the COVID-19 pandemic increased the prevalence of anxiety and depression by 25% worldwide, with more women and young people experiencing these conditions (5). It is well known that changes to daily routines, anxiety about COVID-19 infection, lockdowns, online learning, and social distancing caused by the pandemic had an impact on university students' mental health (6). Several studies have examined the effect of pandemic on college students' mental health and the drivers of greater levels of depression, anxiety, and stress (7-9). For example, a study conducted in Spain, one of the countries hardest hit by the outbreak, discovered that 44.7% of university students had severe anxiety and 31.6% had moderate anxiety (10). Alateq et al., (2020) concluded that 30.2% of students in Saudi Arabia were experiencing significant levels of stress due to the outbreak (11). Another study on college students was conducted by the Higher Education Policy Institute in UK. Accordingly, it has been reported that the rate of worsening mental health after the pandemic among students was 58% (12). Similarly, in a study on university students in France, the rate of students experiencing high levels of anxiety was found to be 16.1% (13), while this rate was found to be 27.7% in Germany (14) and 35% in Poland (15). In line with previous studies conducted in different countries, it was also found that 71.9% of college students reported having significant levels of anxiety due to the COVID-19 pandemic in Türkiye (16). It is noteworthy to add that educating health care students about pandemics in universities can benefit both the students and society as a whole (17).

In many studies, a variety of factors that affected university students' mental health related to the COVID-19 pandemic conditions were examined. These factors include gender, financial loss, inadequate housing, past history of psychiatric follow-up, COVID-19-compatible symptoms, lack of social support, poor social interaction, poor information quality received (18,19), self-emotion evaluation, family relations, reporting worry about COVID-19 caused by the news on social media (20), changes in daily routines, eating habits, and sleeping problems due to the pandemic (21).

There are 23 universities located within the borders of the Turkish Republic of Northern Cyprus , with the Eastern Mediterranean University being the biggest and oldest of all of them. Following the determination of the first case of COVID-19 in Northern Cyprus on March 10, 2020, education was moved online. This unexpected rapid change in education and social life may have resulted in anxiety and depression among students. As per the researchers' knowledge, there are no studies on this field with pharmacy students in Northern Cyprus. In line with previous studies on the mental health of university students following the COVID-19 pandemic, we examined the effects of possible risk factors on depression, anxiety, and stress levels of students. Considering the mental state of university students in the post-pandemic period, it is significant to reach a conclusion that will aid and guide the education and training activities for the students. The present study aimed to investigate the effects of possible factors such as age, gender, the origin of the region, Body Mass Index (BMI), tobacco use, having chronic or psychiatric diseases, relationships with family or friends, anyone diagnosed with COVID-19 in the family, etc., affecting depression, anxiety, and stress levels of pharmacy students at Eastern Mediterranean University.

MATERIAL and METHOD

Sample Population and Questionnaire

A total of 301 pharmacy students who were aged above 18 were included in the study. To achieve the study's aims, a questionnaire was used to conduct a cross-sectional study. Pharmacy students were given a questionnaire with three sections-about their demographics, potential risk factors, and the DAS-21 scale-as part of the research collecting data process. Since English is the primary language for education at the university, the investigators employed an English version of the questionnaire. The survey, which was employed between April and June, 2022, included questions about demographic data (including age, gender, weight, height, the origin of the region, type of pharmacy education, and the semester the students were in), the possible risk factors for depression, anxiety, and stress following the COVID-19 pandemic and the mental health status (i.e., depression, anxiety, and stress) of the participants. Based on the previous studies that examined the factors affecting depression, anxiety, and stress, we included tobacco use, BMI, physical activity, chronic or psychiatric diseases, diagnosis with COVID-19, the severity of the disease, anyone diagnosis with COVID-19 in their family, relationships with family members or friends as the possible risk factors (22-27). Using information from self-reports, we calculated BMI (kg/m2). The mental health status of participants was examined using the Depression, Anxiety, and Stress Scale (DASS-21), which measures three domains (i.e., depression, stress, and anxiety) (21). Each subscale of DASS-21 includes 7 items. Scores for depression, anxiety, and stress subscales of DASS 21 are determined by summing the scores of each item and multiplying the total scores by 2.

Statistical Analysis

Data analysis was employed using the SPSS Statistic 21.0 (IBM SPSS, New York, NY, USA). Frequency and percentage values were used to describe explanatory and outcome variables. Association analysis between groups (e.g., age-depression, tobacco use-anxiety, chronic disease-depression) using non-parametric tests, i.e., Kruskal Wallis, Wilcoxon, and Spearman Correlation tests, were performed for categorical, ordered, or dichotomous variables. When there are several explanatory variables, the odds ratio can be obtained using logistic regression (28). Therefore, Logistic regression analysis was applied to investigate the effects of explanatory variables on the mental health of the students. For the analysis, cut-off categories for severity labels of the depression, anxiety, and stress subscales were classified as follows: 1) normal/mild 2) moderate and 3) severe/extremely severe (29). The significance level for this study was set to 10%, however different significance levels were presented under the tables related to the results.

This study was approved by the Research and Publication Ethics Board of the Eastern Mediterranean University (ETK00-2022-0105). Each participant provided their consent in the study and was fully informed that they might leave the survey at any time without providing a reason.

RESULTS

Descriptive Statistics

A total of 301 respondents who were aged above 18 participated in the survey. Table 1 presents the descriptive statistics of the characteristics of the sample population. The mean age was 22.55+2.57. The majority of the participants were female (66.4%), from the Middle East region (81.1%), and studying in Pharm B (56.1%). The mean semester the students were in was 6.23+2.57. Descriptive statistics of sample characteristics and risk factors of depression, anxiety, and stress following the COVID-19 pandemic are shown in Table 1 and Table 2, respectively.

Accordingly, the majority of the students identified as non-tobacco users (73.1%), had healthy weight (60.5%), and had no chronic (96.0%) or psychological diseases (96.3%). More than half of those surveyed (59.5%) stated that they think COVID-19 is not a scary disease. 60.1% reported that they were not diagnosed with COVID-19, and 20.9% stated that they experienced COVID-19 with mild symptoms. The rate of students whose families were diagnosed with COVID-19 was 68.4%. The mean physical activity duration of the students during the pandemic was reported as 47.58 minutes.

Table 1: Descriptive Statistics of Sample Characteristics

	N	Mean	Std.dev.	%
Sample Characteristics				
Age	300	22.55	2.571	
Gender	301			
Female	200	.34	.473	66.4
Male	101			33.6
Origin of Region	301			
Middle East	244	.19	.406	81.1
Africa	51			16.9
South Asia	2			.7
Type of pharmacy	301			
Pharm B	169	.44	.497	56.1
Pharm D	132			43.9
What semester are you in?	300	6.23	2.573	

Table 2: Descriptive Statistics of Factors Affecting Depression, Anxiety and Stress

Possible affecting factors	N	Mean	Std.dev.	%
Tobacco use	301			
Yes	81	.73	.444	26.9
No	220			73.1
BMI				
Underweight	32			60.5
Healthy	182	.71	1.023	10.6
Overweight	52			17.3
Obese	23			7.6
Physical Activity	300	47.58	38.84	
Do you have any chronic diseases?	301			
Yes	12	.96	.196	4.0
No	289			96.0
Do you have a psychiatric disease?	301			
Yes	11	.96	.188	3.7
No	290			96.3
Do you think that covid-19 is a very scary disease?	301			
Yes	122	.59	.492	40.5
No	179			59.5
Have you been diagnosed with COVID-19?	301			
Yes	120	.60	.490	39.9
No	181			60.1
What was the severity of your disease?	301			
Hospitalized	4			1.3
Severe	23	1.28	1.584	7.6
Mild	63			20.9
Asymptomatic	36			12.0
Have you had anyone diagnosed with COVID-19 in your family?	301			
Yes	206	.32	.466	68.4
No	95			31.6
Do you have any family members who died due to COVID-19?	301			
Yes	45	.85	.357	15.0
No	256			85.0
How was your relationship with your family during the COVID-19 pandemic?	300			
Very bad	3			1.0
Somewhat bad	37			12.3
Same	141	2.51	1.036	46.8
Somewhat good	42			14.0
Very good	77			25.6

Table 2: Descriptive Statistics of Factors Affecting Depression, Anxiety And Stress (Cont.)

Possible affecting factors	N	Mean	Std.dev.	%
How was your relationship with your friends during the COVID-19 pandemic?	300			
Very bad	18			6.0
Somewhat bad	64	2.16	1.134	21.3
Same	124			41.2
Somewhat good	40			13.3
Very good	54			17.9
Have you had anyone in your family who lost his/her job during COVID-19 pandemic?	301			
Yes	52	.83	.379	17.3
No	249			82.7
Do you think that you need psychiatric support due to COVID-19 pandemic?	301			
Yes	57	.81	.392	18.9
No	244			81.1
DASS-21 Scales				
Depression	300			61.8
Normal/Mild	186			21.3
Moderate	64	.55	.764	16.6
Severe/Extremely severe	50			
Anxiety	301			
Normal/Mild	148			49.2
Moderate	68	.79	.856	22.6
Severe/Extremely severe	85			28.2
Stress	301			
Normal/Mild	234			77.7
Moderate	31	.34	.683	10.3
Severe/Extremely severe	36			12.0

15.0% of those had anyone who died due to COVID-19 disease in their family. The majority of the students indicated that their relationship with their family (46.8%) or friends (41.2%) did not change. According to 81.1% of those polled, no one in their family lost their job as a result of the COVID-19 pandemic. The rate of those who stated that they needed psychiatric support was 18.2%.

The means of the depression, anxiety, and stress subscale levels, measured using the DASS-21 scale, were found to be 11.46, 10.75, and 11.75, respectively. Furthermore, 16.6%, 28.2%, and 12.0% of those surveyed were found to experience severe/extremely severe depression, anxiety, and stress, respectively.

Logit Estimates for Depression, Anxiety, and Stress Among Pharmacy Students Following The COVID-19 Pandemic

Table 3 and 4 tabulates the logit estimates results of depression, anxiety, and stress among pharmacy students following the COVID-19 pandemic. The results are presented with β, standard errors, and odds ratios. For the depression subscale, having a psychiatric disease was a significant positive predictor of severe/extremely severe depression. The odds of students having a higher level of depression were 5.87 times higher for those who had the psychiatric disease as compared to those who did not have the disease. The relationship with family members or friends during the COVID-19 pandemic was also found to be a significant positive predictor of depression.

Accordingly, the log odds of being in a higher level of depression were 3.96 times greater for those who had a somewhat bad relationship with the family members, 2.46 times greater for those who had the same relationship with the family members, and 2.58 times greater for those who had a somewhat good relationship with the family members

Table 3: Logit Estimates for Depression, Anxiety, Stress

(1)Severe/Extreme

	Depression		*Anxiety*		*Stress*	
Sample characteristics:	β (SE)	OR	β (SE)	OR	β (SE)	OR
Age	-.91 (.068)	.913	-.036 (.058)	.965	.019 (.072)	1.019
Gender[a]						
Female	.545 (.331)	1.72	.509 (.300)*	.1.664	-.032 (.416)	.968
Origin of Region[b]						
Middle East	-1.603 (1.564)	.201	.004 (1.392)	1.004	-2.106 (1.482)	.122
Africa	-1.990 (1.610)	.137	-.256 (1.422)	.774	-2.031 (1.526)	.131
Type of pharmacy education[c]						
Pharm B	-.025 (.316)	.975	.632 (.309)**	1.881	-.163 (.403)	.849
What semester are you in?	-.106 (.065)	.900	-.119 (.062)*	.888	-.230 (.082)***	.795

Note: Reference categories of explanatory variables are (a) male; (b) South Asia; (c) Pharm D. Response variables were categorized as (a) normal/mild, (b) moderate, (c) severe/extreme.
*** p<0.01; ** p<0.05; * p<0.1.

Table 4: Logit Estimates for Depression, Anxiety, Stress

	(1)Severe/Extreme					
	Depression		*Anxiety*		*Stress*	
Possible risk factors:	β (SE)	OR	β (SE)	OR	β (SE)	OR
Tobacco use[d]						
Yes	.221 (.346)	1.247	.634 (.319)**	1.884	.912 (.404)**	2.488
BMI[e]						
Underweight	.030 (.579)	1.031	-.429 (.525)	.651	-1.246 (.578)**	.288
Healthy	.036 (.693)	1.037	-1.294 (.656)**	.274	-1.453 (.771)*	.234
Overweight	-.060 (.653)	.942	-.589 (.587)	.555	-2.230 (.710)***	.108
Physical Activity	.003 (.004)	1.003	-.001 (.004)	.999	.004 (.005)	1.004
chronic diseases[f]						
Yes	-.923 (1.084)	.398	1.015 (.725)	.2.760	-1.542 (1.208)	.214
psychiatric disease[g]						
Yes	1.770 (.849)**	5.870	2.065 (.946)**	7.888	3.387 (.941)***	29.58
COVID-19 is a very scary disease[h]						
Yes	.459 (.279)	1.582	.366 (.268)	1.442	.216 (.358)	1.241
diagnosed with COVID-19[i]						
Yes	.424 (1.220)	1.528	1.254 (1.006)	3.506	.666 (1.425)	1.945
the severity of your disease[j]						
Hospitalized	-1.150 (1.445)	.317	-1.355 (1.21)	.258	-.508 (1.608)	.602
Severe	.354 (.6446)	1.424	-.023 (.586)	.977	.236 (.715)	1.266
Mild	.032 (.5446)	1.032	-.108 (.469)	.898	-.510 (.647)	.601
anyone diagnosed with COVID-19 in your family[k]						
Yes	.377 (.3407)	1.457	.990 (.317)***	2.692	.587 (.423)	1.799
any family members who died due to COVID-19[l]						
Yes	.272 (.393)	1.312	.210 (.388)	1.234	.279 (.484)	1.322

Note: Reference categories of explanatory variables are (d) no; (e)obese; (f-i) no ; (j) asymptomatic (k-l) no. Response variables were categorized as (a) normal/mild, (b) moderate, (c) severe/extreme.
*** p<0.01; ** p<0.05; * p<0.1.

Table 4: Logit Estimates for Depression, Anxiety, Stress (Cont.)

(1)Severe/Extreme						
	Depression		Anxiety		Stress	
Possible risk factors:	β (SE)	OR	β (SE)	OR	β (SE)	OR
Relationship with family during the COVID-19 pandemic[m]						
Very bad	2.09 (.199)	1.22	.098 (1.594)	1.103	1.517 (1.676)	4.56
Somewhat bad	1.378 (.633)**	3.966	1.025 (.554)*	2.787	2.046 (.779)***	7.73
Same	.900 (.492)*	2.460	.119 (.422)	1.126	.711 (.614)	2.035
Somewhat good	.951 (.513)*	2.587	.387 (.458)	1.473	.688 (.627)	1.989
Relationship with friends during the COVID-19 pandemic?[n]						
Very bad	-.478 (.793)	.620	-1.064 (.825)	.345	-1.303 (.986)	.272
Somewhat bad	-.927 (.584)	.396	-.475 (.529)	.622	-1.645 (.756)**	.193
Same	-.651(.540)***	.192	-.379 (471)	.684	-1.513 (.691)**	.220
Somewhat good	-.558 (.506)	.573	.248 (.478)	1.282	.048 (.614)	1.050
Anyone in the family who lost his/her job during COVID-19 pandemic[o]						
Yes	.981 (.370)***	2.666	1.190 .366)***	3.287	1.012 (.456)**	2.752
need psychiatric support due to COVID-19 pandemic?[p]						
Yes	1.314(.342)***	3.721	.969 (.347)***	2.636	1.405 (.420)**	4.076
Pseudo R2		.166		.158		.219
N		301		301		301

Note: Reference categories of explanatory variables are (m-n) very good; (o-p) no. Response variables were categorized as (a) normal/mild, (b) moderate, (c) severe/extreme.

*** p<0.01; ** p<0.05; * p<0.1.

The relationship with the friends during COVID-19 was a significant negative predictor of depression. The odds of being at a higher level of depression were 0.192 times less for those who had the same relationship with their friends during COVID-19 pandemic. Students who had a family member who lost his or her job during the pandemic were 2.67 times more likely to have a higher level of depression as compared to those who did not have a family member who lost his or her job. A need for psychiatric support due to the COVID-19 pandemic was found to be a significant positive predictor of depression. The odds of having a higher level of depression were found to be 3.72 times greater for those who needed psychiatric support as compared to those who did not. However, any other variables that were included in the analysis were found to be insignificant predictors of depression.

As shown in Table 3, the findings revealed that gender was a significant factor affecting the level of anxiety among students. The odds of a student identified as female being at a higher level of anxiety was1.66 times that of a student identified as male. Moreover, the odds of being in a higher level of anxiety were found to be 1.88 times higher among students who were Pharm B (5 years undergraduate program) as compared to those students who were Pharm D (6 years undergraduate program). It was discovered that the semester the students were in was a significant and negative predictor of anxiety. Accordingly, the odds ratio indicates that the odds of being in a higher category on anxiety decrease by a factor of .888 for every one-unit increase in the number of semesters. Lifestyles, e.g., tobacco use and BMI, of the students were significant predictors of anxiety. The results showed that students who were tobacco users were 1.88 times more likely to be in a higher level of anxiety as compared to the students who were non-tobacco users. A healthy weight is also a significant negative factor affecting the level of anxiety. The odds of a student identified as healthy having a higher level of anxiety were .274 times higher than those of a student identified as obese. Having a psychiatric disease is a crucial factor for anxiety similar to depression. The odds of being at a higher level of anxiety were 7.89 times greater among students who indicated that they had a psychiatric disease. Students who had a family member diagnosed with COVID-19 had 2.69 times the odds of having a greater level of anxiety than those who did not have anyone diagnosed with COVID-19 in their family. The odds of having a greater level of anxiety were 2.79 times higher for students who had a relatively negative relationship with their family than those who had a very good relationship. Students who had a family member who lost his or her job during the pandemic were 3.29 times more likely to be anxious than those who did not have a family member who lost his or her job. The requirement for psychiatric support in the context of the COVID-19 pandemic was discovered to be a significant positive predictor of anxiety. Accordingly, the odds of having a higher degree of anxiety were found to be 2.64 times higher for individuals who needed psychiatric support than those who did not.

The logit estimates for stress are presented in Tables 3 and 4. Accordingly, the semester students were in was found as a significant negative predictor of stress. The odds ratio indicates that the odds of being in a higher category on stress decrease by a factor of .888 for every one-unit increase in the number of semesters. Similar to the anxiety subscale, students who were tobacco users were 2.48 times more likely to be in a higher level of stress as compared to the students who were non-tobacco users. A healthy weight is also a significant negative factor influencing stress levels. For each unit increase in BMI category (from underweight to obese), the log odds of being stressed decrease by .288, .234, and .108, respectively. We also observed that students who stated that they had a psychiatric disease were 29.58 times more likely to experience stress. The odds of being in a higher level of stress were 7.73 times higher for those students whose relationship with their family was somewhat bad as compared to those students whose relationship was very good. On the other hand, for one unit increase in the relationship with the friends' categories, we expect a .193 and .220 decrease in the ordered log odds of being in a higher level of stress, respectively. Students who had a family member who lost his/her job during the pandemic were 2.75 times more likely to feel stressed than those who did not have a family member who lost his/her job. Psychiatric support due

to the COVID-19 pandemic was found to be another important predictor of the stress subscale. Accordingly, it was found to lead to 4.08 times more stress for those students who needed psychiatric support compared to those who did not need it.

DISCUSSION

Concerning the COVID-19 pandemic's psychological and environmental effects on students' educational experiences, there are still many undetermined issues (8). By conducting a survey among 301 pharmacy students, the current study examined the prevalences of depression, anxiety, and stress and the effects of possible risk factors on their psychological health following the COVID-19 pandemic. Based on the findings, the main results of the present study showed that the prevalences of severe/extremely severe depression, anxiety, and stress were found to be 16.6%, 28.2%, and 12.0%, respectively.

The effect of gender differences on the pharmacy students' depression, anxiety, and stress levels was only found to be significant for anxiety. Accordingly, female pharmacy students were more likely to have a higher anxiety level compared to male students. Parallel to these findings, previous studies on the subject reported that anxiety levels were higher among female university students than males (30). While students who are Pharm B students were more likely to feel anxious than their Pharm D counterparts, students with a higher academic year were found to be less anxious and stressed than those with a lower academic year. A study conducted on the academic stress of college students reported that freshmen and sophomores had higher mean stress levels than juniors and seniors (31). It is important to highlight that students with a higher academic year could have less academic pressure and, therefore, less anxiety and stress about the future.

The findings showed that tobacco use was a significant contributor to anxiety and stress among pharmacy students. Besides being one of the leading causes of death and morbidity in the world (32), smoking has also been linked in numerous studies to psychiatric disorders such as anxiety, depression, and stress (33). Three non-mutually exclusive models for the smoking-anxiety relationship were proposed by Moylan et al. (2012): (1) smoking may make people more likely to feel anxious; (2) anxiety may make people more likely to smoke; and (3) rates of both smoking and anxiety may be influenced by a common vulnerability variable (34).

In our study, people with psychiatric diseases were found to be significantly more likely to experience depression, anxiety, and stress. In line with these findings, other studies have also found similar results. A study conducted by Hao et al. (2020) showed that psychiatric patients were more likely to experience depression, anxiety, and stress due to the COVID-19 pandemic (35). These people with psychiatric diseases may not have visited psychiatrists as a result of the lockdown due to insufficient health services during COVID-19 in hospitals. People with psychiatric illnesses were more likely to experience higher levels of depression, anxiety, and stress, according to a different study using multiple regression analysis to examine the depression, anxiety, and stress levels among physicians during the COVID-19 pandemic (36).

One-fourth of those polled indicated that the COVID-19 pandemic strained relationships with their family members and/or their friends. The regression results showed that those students who reported a somewhat bad relationship with family or friends were found to be more susceptible to experiencing extremely severe and/or severe depression, anxiety, and stress. Possibly, increased stressors at home, a lack of communication with friends, and social isolation due to the COVID-19 pandemic may have caused the students to be more prone to have higher depression, anxiety, and stress levels (37).

We found a significant effect of family members' loss of jobs during the pandemic on having higher depression, anxiety, and stress levels among pharmacy students. The COVID-19 pandemic is well

known for having significantly increased unemployment rates across a number of countries globally (38). It has been challenging for people to access financial resources as a result of their loss of employment. Any family member's job loss during the pandemic may also play a significant role in the reporting of severe depression, anxiety, and stress symptoms among university students.

Our findings specifically indicate that students who had lower BMI values were less likely to have extremely severe and/or severe anxiety and stress levels compared to the students who were obese. Early data from the COVID-19 pandemic suggested that specific patient traits were linked to higher morbidity and mortality from SARS-CoV-2 (39). The most common recorded risk factors among these characteristics were older age, male sex, smoking, the existence of chronic medical disorders, and obesity (BMI 30 kg/m2) (40,41). A study conducted in France also showed a positive association between a higher BMI and the severity of COVID-19 infection (42). Therefore, it is inevitable for people with a higher BMI to feel more anxious and stressed about their health due to COVID-19. Moreover, it has also been shown that the death of a parent or a friend may have caused psychological distress, and research has indicated that those who are overweight may be more susceptible to such stresses than those who are of normal weight (43).

The results showed that students who had any family members diagnosed with COVID-19 were more likely to feel anxious than their counterparts who had no one diagnosed with COVID-19 in their family. A study conducted with 90 participants in Türkiye showed that the probability of anxiety and depression among COVID-19 patient relatives in the intensive care unit during the pandemic was much greater than that of patient relatives without COVID-19 (44). This outcome was also reflected in the current work, since our results also pointed out that the experience of a family member diagnosed with the disease negatively affected mental well-being without regard to gender. Since the breakdown of the family in various facets of life is caused by the death of a family member (45), fear of losing a family member might be among the reasons that can increase a person's anxiety level.

Those participants who need psychiatric support due to the COVID-19 pandemic were found to be more depressed, anxious, and stressed than participants who do not need any psychological support. It is undoubtedly helpful to discuss their experiences, psychological issues, and worries with a friend, a relative, or a health care practitioner. This can assist in lessening their feelings of depression, anxiety, and stress (37; 46).

CONCLUSION

College students and the general public have both been under stress as a result of the COVID-19 pandemic, which has been identified as a global public health crisis since the end of 2019. Due to these pandemic-related stresses and constraints in social life, it has been shown that university students are more likely to have mental health issues, which might have a negative impact on their academic performance and socialization. This study found that among pharmacy students, there were signs of stress, anxiety, and depression related to the COVID-19 pandemic. The study results have been found to be associated different lifestyles, demographics, and COVID-19-related variables. In line with previous studies on this subject, being female, academic year, tobacco use, Body Mass Index (BMI), history of psychological disease, any relatives diagnosed with COVID-19, relationship with family or friends, any relatives who lost their job during COVID-19, and need for psychological support were found to be factors associated with one or more mental health issues such as depression, anxiety, and stress that increased the risks of depression. The results obtained from our study are relevant not only in relation to the COVID-19 pandemic but also, more generally, in the response of college students in Northern Cyprus to COVID-19 and its effect on mental health.

The outcomes of this research study have been found to be in parallel with the literature's findings. Based on these, the change in depression, anxiety, and stress levels of college students following the

COVID-19 pandemic should be cross-checked to further observe the weakening of the negative effects of the pandemic. Moreover, the data provided is also valuable to be used at the earlier stages of possible world-wide pandemics to overcome similar negative effects.

Declaration of Ethical Code: In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions against Scientific Research and Publication Ethics" are not carried out.

This study was approved by the Research and Publication Ethics Board of the Eastern Mediterranean University (ETK00-2022-0105). Each participant provided their consent in the study and was fully informed that they might leave the survey at any time without providing a reason.

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

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Trombositopenisi Olan Karaciğer Sirozu Hastalarında Dalak Boyutunun Lökosit ve Trombosit Düzeyleri Üzerindeki Etkisinin Değerlendirilmesi: Retrospektif Tek Merkezli Bir Çalışma

Evaluation of the Effect of Spleen Size on Leukocyte and Platelet Levels in Liver Cirrhosis Patients With Thrombocytopenia: A Retrospective Single-Center Study

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ÖZ

Giriş: Karaciğer sirozu hastalarında sitopeniler klinik bir problem olarak hasta takiplerinde ortaya çıkabilmektedir. Biz bu çalışmada trombosit sayısı 100 bin/mikrolitre'nin altında olan karaciğer sirozu hastalarında, dalak boyutları ile trombosit/WBC/nötrofil/lenfosit/monosit düzeyleri arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık. Materyal ve Metot: Hastalar, dalak boyutlarına göre 4 gruba ayrıldı. Dalak boyutu normal olarak bildirilmiş olan hastalar (Dalak uzunluğu ≤13 cm(santimetre) olan hastalar da bu gruba dahil edildi) birinci grup, dalak uzunluğu 13 cm-15 cm arasında olanlar (13 cm dahil değil, 15 cm dahil değil) ikinci grup, dalak uzunluğu 15 cm – 18 cm arasında olanlar (15 cm dahil, 18 cm dahil değil) üçüncü grup, dalak uzunluğu ≥18 cm olanlar dördüncü grup olarak sınıflandırıldı. Gruplar arasında WBC, nötrofil, lenfosit, monosit düzeylerine göre farklılık olup olmadığı araştırıldı. Bulgular: Dalak uzunluğu ≥18 cm olanlarda dalak uzunluğu <15 cm olanlara göre trombosit düzeyinin istatistiksel olarak anlamlı düzeyde daha düşük olduğu görüldü (p<0,05). Dalak uzunluğu ≥15 cm olanlarda dalak uzunluğu <15 cm olanlara göre WBC, lenfosit ve monosit düzeylerinin istatistiksel olarak anlamlı düzeyde daha düşük olduğu bulundu (p<0,05). Tartışma: Dalak uzunluğu <15 cm olan karaciğer sirozu hastalarında lökopeni/trombositopeni hemen siroza bağlanmamalıdır ve o durumlarda sitopeniye yol açabilecek diğer potansiyel sebepler de akılda tutulmalıdır.

Anahtar Kelimeler: *Karaciğer sirozu, Splenomegali, Lenfopeni, Nötropeni, Trombositopeni*

ABSTRACT

Introduction: In patients with liver cirrhosis, cytopenias may occur as a clinical problem during patient follow-up. In this study, we aimed to evaluate whether there is a relationship between spleen size and platelet/WBC/neutrophil/lymphocyte/monocyte levels in liver cirrhosis patients who had platelet counts below 100 thousand/microliter. Material & Methods: The patients were classified into 4 groups according to their spleen size. Patients whose spleen size was reported to be normal (patients with spleen length ≤13 cm (centimeters) were also included in this group) were classified as group 1, patients with a spleen length between 13-15 cm (13 cm not included, 15 cm not included) were classified as group 2, those with a spleen length between 15 cm - 18 cm (15 cm included, 18 cm not included) were classified as group 3, and those with a spleen length ≥18 cm were classified as group 4. It was investigated whether there were differences between the groups in terms of WBC, neutrophil, lymphocyte and monocyte levels. Results: It was observed that platelet level was statistically significantly lower in patients with spleen length ≥18 cm compared to those with spleen length <15 cm (p<0.05). It was found that WBC, lymphocyte and monocyte levels were statistically significantly lower in patients with spleen length ≥15 cm compared to those with spleen length <15 cm (p<0.05). Discussion: Leukopenia/thrombocytopenia should not be immediately attributed to cirrhosis in liver cirrhosis patients with spleen length <15 cm, and other potential cytopenia causes should also be kept in mind in those situations.

Keywords: *Liver cirrhosis, Splenomegaly, Lymphopenia, Neutropenia, Thrombocytopenia*

GİRİŞ

Karaciğer sirozunda portal hipertansiyon ve splenomegali görülebilmektedir. Portal hipertansiyonu olan karaciğer sirozlu olgularda zaman içerisinde sitopeniler gelişebilmektedir. Lv Y ve ark. 183 portal hipertansiyonu olan karaciğer sirozlu hastada yaptıkları çalışmada, periferal sitopeni sebebi olarak; %80,5 sadece hipersplenizm olduğunu, %3,5 hipersplenizm dışı faktörler olduğunu, %16 hipersplenizm ile hipersplenizm dışı faktörlerin birlikte etkili olduğunu bildirmişlerdir (1). Lu YF ve ark. da, azalmış periferal kan hücre sayımı olan 322 sirotik portal hipertansiyon hastasında yaptıkları çalışmada, hastaların %27,6'sında pansitopeni olduğunu bildirmişlerdir (2). Lu YF ve ark. da, azalmış periferal kan hücre sayımı olan 322 sirotik portal hipertansiyon hastasında yaptıkları çalışmada, 206 hastada WBC (white blood cell) düzeyinin $<4{,}0x10^9$/L olduğunu bildirmişlerdir (2).

Splenomegali, Lugano Klasifikasyonu'nda 13 cm'in üzerinde dalak boyutu olarak kabul edilmiştir (3). Biz bu çalışmada trombosit düzeyi 100 bin/mikrolitre'nin altında olan karaciğer sirozu hastalarında, dalak boyutları ile trombosit seviyeleri arasında bir ilişki olup olmadığını araştırmayı amaçladık. Ek olarak, trombosit düzeyi 100 bin/mikrolitre'nin altında olan karaciğer sirozu hastalarında, WBC, nötrofil, lenfosit ve monosit düzeylerinin dağılımlarını ölçmeyi ve dalak boyutu ile lökopeniler arasında bir ilişki olup olmadığını araştırmayı da amaçladık.

GEREÇ ve YÖNTEM

SDÜ Tıp Fakültesi Hastanesi (SDÜ Araştırma ve Uygulama Hastanesi)'nde 01.01.2015 ve 30.04.2024 tarihleri arasında (01.01.2015 ve 30.04.2024 tarihleri dahil) hemogram testi vermiş olan 115 hasta çalışmaya alındı. Çalışmaya hastane dosya arşivinde veya elektronik arşivinde karaciğer sirozu tanısı olduğu bilinen hastalar alındı. 19 yaş ve üzerinde olan hastalar çalışmaya alındı. Trombosit düzeyi 100 bin/mikrolitre'nin altında olan hastalar çalışmaya alındı. 19 yaşının altındaki hastalar çalışmaya alınmadı. Trombosit düzeyi 100 bin/mikrolitre veya üzerinde olan hastalar çalışmaya alınmadı. Bilinen lenfoma hastalığı olan hastalar çalışmaya alınmadı. Bilinen myeloproliferatif hastalığı olan hastalar çalışmaya alınmadı. Talasemi major hastaları ve bilinen lösemi tanısı olan hastalar çalışmaya alınmadı. Dalak boyutu ultrasonografik olarak ölçüldüğü esnada, aktif tüberküloz veya brucella enfeksiyonu olduğu bilinen hastalar da çalışmaya alınmadı. Aplastik anemi öyküsü olan hastalar, kök hücre nakli öyküsü olan hastalar, myelodisplastik sendrom (MDS) tanısı olan hastalar, myeloid neoplasm öyküsü olan hastalar, immün trombositopenisi (ITP) hastaları, premalign klonal sitopeni tanısı koyulmuş olan hastalar da çalışmaya alınmadı. Karaciğer nakli olan hastaların nakil sonrası verileri çalışmaya alınmadı, nakil öncesi verileri alındı. Splenektomi yapılmış olan hastalar da çalışmaya alınmadı.

Hastalardan, dalak boyutlarının en son ölçümüne en yakın tarihli olan hemogram tahlilini verdiği günden önceki son 30 gün içerisinde veya hemogram tahlilini verdiği günden sonraki ilk 30 gün içerisinde hastanemiz laboratuvar Vitamin B12 testi sonucu alt referans limitinin altında vitamin B12 düzeyi sonucu olduğu dosyasında tespit edilenler (belirtilen dönemlerde hastanemizde vitamin B12 sonucu olup sonucu hastanemiz laboratuvar Vitamin B12 tetkiki alt referans limitinin altında olduğu tespit edilenler), en yakın hemogram tahlilini verdiği günden önceki son 30 gün içerisinde veya hemogram tahlilini verdiği günden sonraki ilk 30 gün içerisinde hastanemiz laboratuvar Folik asit düzeyi testi sonucu <2 ng/mL olduğu dosyasında tespit edilenler (belirtilen dönemlerde hastanemizde Folik asit düzeyi sonucu olup sonucu <2 ng/mL olduğu dosyasında tespit edilenler), kemik iliğini infiltre eden bir hastalığı olduğu dosyasında görülenler, bilinen AIDS (Acquired Immune Deficiency Syndrom) tanısı olanlar, bilinen HIV (Human immunodeficiency virus) enfeksiyonu olanlar da çalışmaya dahil edilmedi. Dalak boyutlarının en son ölçümüne en yakın tarihli hemogram tahlilini verdiği gün akut enfeksiyon tanısı olduğu dosyasında görülen hastaların en yakın tarihli hemogram tahlili çalışmaya alınmayıp, onun yerine akut enfeksiyon tanısı olmayan en yakın diğer hemogram tahlili çalışmaya alındı.

Çalışmaya alınan tüm hastaların, hastane dosyaları veya elektronik hasta arşivlerindeki raporlu/kayıtlı en son ölçülmüş olan dalak boyutları kaydedildi. Hastaların dalak boyutunun en son ölçümüne en yakın tarihli olan hemogram parametrelerinden WBC (White blood cell (Beyaz küre)), nötrofil, lenfosit, monosit ve plt (trombosit) değerleri kaydedildi ve bu değerlerin ortanca (Median) ve Ortalama (Mean) değerleri hesaplandı; sonrasında bulgular tablolar halinde de bildirildi.

Hastalar, dalak boyutlarına göre 4 gruba ayrıldı. Dalak boyutu normal olarak bildirilmiş olan hastalar (Dalak uzunluğu ≤13 cm (santimetre) olan hastalar da bu gruba dahil edildi) birinci grup, dalak uzunluğu 13 cm-15 cm arasında olanlar (13 cm dahil değil, 15 cm dahil değil) ikinci grup, dalak uzunluğu 15 cm-18 cm arasında olanlar (15 cm dahil, 18 cm dahil değil) üçüncü grup, dalak uzunluğu ≥18 cm olanlar dördüncü grup olarak sınıflandırıldı. Her grup hastanın mean ve median trombosit değerleri hesaplandı ve gruplar arasında trombosit düzeylerine göre farklılık olup olmadığı araştırıldı. Bununla birlikte, her grup hastanın mean ve median WBC, nötrofil, lenfosit, monosit değerleri de hesaplandı ve gruplar arasında WBC, nötrofil, lenfosit, monosit düzeylerine göre farklılık olup olmadığı da araştırıldı.

Çalışma retrospektif bir çalışma olduğu için, sadece SDÜ Tıp Fakültesi Hastanesi (SDÜ Araştırma ve Uygulama Hastanesi) ‘‘elektronik/eski tip dosya’’ arşiv kayıtlarında olduğu görülen bulgular/tanılar/hasta özellikleri/hasta tetkik sonuçları/hasta takip notları/hasta bilgileri çalışmada kullanıldı. Dışlama faktörleri değerlendirilirken ise, SDÜ Tıp Fakültesi Hastanesi ‘‘elektronik/eski tip dosya’’ arşiv kayıtlarında mevcut olan bulgular/tanılar/hasta özellikleri /hasta tetkik sonuçları/hasta takip notları/hasta bilgileri arasında kayıtlı olduğu gözlenen herhangi bir dışlama faktörü mevcut olan hastalar çalışmaya alınmadı. Diğer yandan, SDÜ Tıp Fakültesi Hastanesi ‘‘elektronik/eski tip dosya’’ arşiv kayıtlarında mevcut olan bulgular/tanılar/hasta özellikleri /hasta tetkik sonuçları/hasta takip notları/hasta bilgileri arasında kayıtlı olduğu gözlenen herhangi bir dışlama faktörü mevcut olmayan hastalar çalışmaya alındı.

Çalışma için T.C. Süleyman Demirel Üniversitesi Sağlık Bilimleri Etik Kurulu’ndan 01.08.2024 tarihli ve 78/16 sayılı onay alındı.

İstatistiksel analiz

İstatistiksel analizler SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) adlı paket program kullanılarak yapılmıştır. Bulguların yorumlanmasında frekans tabloları ve tanımlayıcı istatistikler kullanılmıştır. Normal dağılıma uygun olmayan ölçüm değerleri için parametrik olmayan yöntemler kullanılmıştır. Parametrik olmayan yöntemlere uygun şekilde, üç veya daha fazla bağımsız grubun ölçüm değerleriyle karşılaştırılmasında “Kruskal-Wallis H” test (χ2-tablo değeri) yöntemi kullanılmıştır. Anlamlı fark çıkan değişkenlerin ikili karşılaştırılmalarında “Bonferroni düzeltmesi” kullanılmıştır. İki nitel değişkenin birbiriyle ilişkilerinin incelenmesinde “Pearson-χ2” çapraz tabloları kullanılmıştır. Normal dağılıma sahip olmayan verilerde iki nicel değişkenin ilişkilerinin incelenmesinde “Spearman” korelasyon katsayısı kullanılmıştır.

BULGULAR

Dalak boyutu gruplarına göre WBC değerleri açısından istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p<0,05$) (Tablo 1). Anlamlı farkın hangi gruptan kaynaklandığını tespit etmek için yapılan Bonferroni düzeltmeli ikili karşılaştırmalar sonucunda; 1. grup ile 3 ve 4. grup arasında anlamlı farklılık tespit edilmiştir. 1. gruptakilerin WBC değerlerinin, 3 ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir. Aynı şekilde, 2. grup ile 3. ve 4. grup arasında anlamlı farklılık tespit edilmiştir. 2. gruptakilerin WBC değerleri, 3. ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir (Tablo 1).

Dalak boyutu gruplarına göre nötrofil değerleri açısından istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p<0,05$). Anlamlı farkın hangi gruptan kaynaklandığını tespit etmek için yapılan

Bonferroni düzeltmeli ikili karşılaştırmalar sonucunda; 1. ve 2. grup ile 4. grup arasında anlamlı farklılık tespit edilmiştir. 1. ve 2. gruptakilerin nötrofil değerlerinin, 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir (Tablo 1).

Dalak boyutu gruplarına göre lenfosit değerleri açısından istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p<0,05$). Anlamlı farkın hangi gruptan kaynaklandığını tespit etmek için yapılan Bonferroni düzeltmeli ikili karşılaştırmalar sonucunda; 1. grup ile 3. ve 4. grup arasında anlamlı farklılık tespit edilmiştir. 1. gruptakilerin lenfosit değerlerinin, 3. ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir. Aynı şekilde, 2. grup ile 3. ve 4. grup arasında da anlamlı farklılık tespit edilmiştir. 2. gruptakilerin lenfosit değerlerinin de 3. ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir (Tablo 1).

Dalak boyutu gruplarına göre monosit değerleri açısından istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p<0,05$). Anlamlı farkın hangi gruptan kaynaklandığını tespit etmek için yapılan Bonferroni düzeltmeli ikili karşılaştırmalar sonucunda; 1. grup ile 3. ve 4.grup arasında anlamlı farklılık tespit edilmiştir. 1. gruptakilerin monosit değerlerinin, 3. ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir. Aynı şekilde, 2. grup ile 3. ve 4. grup arasında da anlamlı farklılık tespit edilmiştir. 2. gruptakilerin monosit değerleri de 3. ve 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu da belirlenmiştir (Tablo 1).

Dalak boyutu sınıflarına göre platelet değerleri açısından da istatistiksel olarak anlamlı farklılık tespit edilmiştir ($p<0,05$). Anlamlı farkın hangi gruptan kaynaklandığını tespit etmek için yapılan Bonferroni düzeltmeli ikili karşılaştırmalar sonucunda; 1. ve 2. grup ile 4. grup arasında anlamlı farklılık tespit edilmiştir. 1. ve 2. gruptakilerin platelet değerlerinin, 4. grupta olanlara göre anlamlı düzeyde daha yüksek olduğu belirlenmiştir (Tablo 1).

Tablo 1: Dalak Boyutu Gruplarına Göre Bazı Hemogram Parametrelerinin Karşılaştırılması

Dalak boyutu / **Değişken**	**1. grup (n=22)**		**2. grup (n=26)**		**3. grup (n=41)**		**4. grup (n=26)**		**İstatistiksel analiz*** **Olasılık**
	$\bar{X}$ ± S.S.	**Medyan (IQR)**	**$\bar{X}$ ± S.S.**	**Medyan (IQR)**	**$\bar{X}$ ± S.S.**	**Medyan (IQR)**	**$\bar{X}$ ± S.S.**	**Medyan (IQR)**	
WBC	4622,72±1950,08	4250,0 (2325,0)	4530,76±1705,46	4400,0 (3000,0)	3224,39±1106,74	3400,0 (2000,0)	3000,00±1037,30	3150,0 (1425,0)	χ^2=20,174 **p<0,001** **(1-3,4)** **(2-3,4)**
Nötrofil	2768,18±1415,35	2450,0 (1350,0)	2688,46±1229,41	2300,0 (2050,0)	2046,34±862,87	2000,0 (1450,0)	1934,61±780,22	1900,0 (1025,0)	χ^2=8,652 **p=0,034** **(1,2-4)**
Lenfosit	1136,36±418,09	1100,0 (650,0)	1107,69±535,85	1000,0 (950,0)	700,00±261,72	700,0 (400,0)	650,00±347,85	650,0 (500,0)	χ^2=27,465 **p<0,001** **(1-3,4)** **(2-3,4)**
Monosit	540,91±301,83	500,0 (500,0)	569,23±251,03	500,0 (425,0)	351,21±171,93	300,0 (300,0)	276,92±117,67	300,0 (125,0)	χ^2=27,534 **p<0,001** **(1-3,4)** **(2-3,4)**
Platelet	75318,18±20522,66	82500,0 (33000,0)	73076,92±18200,92	72500,0 (31250,0)	64975,60±22706,26	68000,0 (38500,0)	58307,69±22019,57	54000,0 (38250,0)	χ^2=10,208 **p=0,017** **(1,2-4)**

*Normal dağılıma sahip olmayan verilerde üç veya daha fazla bağımsız grubun ölçüm değerleriyle karşılaştırılmasında "Kruskal-Wallis H" test (χ^2-tablo değeri) istatistikleri kullanılmıştır.

Dalak uzunluğu ≥18 cm olanlarda dalak uzunluğu <15 cm olanlara göre trombosit düzeyinin istatistiksel olarak anlamlı derecede daha düşük olduğu görüldü (p<0,05). Dalak uzunluğu ≥18 cm olanlarda dalak uzunluğu <15 cm olanlara göre nötrofil düzeyinin de istatistiksel olarak anlamlı derecede daha düşük olduğu da görüldü (p<0,05). (Tablo 1).

Dalak boyutu >13 cm olanlarda yapılan ayrı bir analizde ise dalak boyutu >13 cm olan hastalarda, dalak boyutu ile WBC, nötrofil, lenfosit, monosit ve platelet değeri arasında negatif yönde, zayıf derecede ve istatistiksel olarak anlamlı ilişki tespit edilmiştir (p<0,05). Dalak boyutu arttıkça, WBC, nötrofil, lenfosit, monosit ve platelet değerleri azalmaktadır (Tablo 2).

Tablo 2: Dalak Boyutu >13 cm Olanlarda Dalak Boyutu ile WBC/Nötrofil/Lenfosit/Monosit/Platelet Düzeyleri Arasındaki İlişkilerin İncelenmesi

Korelasyon*	**Dalak boyutu**	
	r	***p***
WBC	-0,362	**<0,001**
Nötrofil	-0,260	**0,012**
Lenfosit	-0,390	**<0,001**
Monosit	-0,468	**<0,001**
Platelet	-0,324	**0,002**

*Normal dağılıma sahip olmayan verilerde iki nicel değişkenin ilişkilerinin incelenmesinde "Spearman" korelasyon katsayısı kullanılmıştır.

TARTIŞMA ve SONUÇ

Karaciğer sirozunda sitopeni ve trombositopeni nedeni olarak bilinen başlıca etkenlerden birisi hipersplenizmdir. Aster RH. splenomegalide dalaktaki trombosit havuzunun büyük oranda artabileceğini 1966 yıldırında bildirdi (4). Bununla birlikte, trombopoietin (TPO) trombosit üretimini ve artmasını sağlayan bir moleküldür ve karaciğerden de sentezlenmektedir (5-7). Martin TG 3rd ve ark. yaptıkları çalışmada 44 sirozlu hastanın 39 unda trombopoietin düzeyinin tespit edilemediğini bildirmişlerdir (8). 17 hastanın 16'sında da karaciğer nakli sonrasında trombopoietin düzeylerinin tespit edilebildiğini belirtmişlerdir (8). Çalışmamızda da dalak boyutu normal olan karaciğer sirozu hastalarında da sitopenilerin görülmesi nedeni ile karaciğer sirozu olan hastalarda sitopenilerin sadece hipersplenizme bağlanmaması gerektiği desteklendi.

Gschwantler M ve ark. transjugular intrahepatic portosystemic shunt (TIPS) ile portal dekompresyon sonrasında trombosit düzeylerindeki değişikliği gözlemlemek amacı ile prospektif kontrollü bir çalışma yapmışlardır (9). Gschwantler M ve ark.'in yaptığı çalışmada 55 TIPS hastası ile shunt olmayan 110 kontrol grubu karşılaştırıldığında, TIPS sonrası 1. aydan 12. aya kadar olan takiplerde TIPS grubunda trombosit düzeylerinin anlamlı derecede daha yüksek olduğunu gözlemlemişlerdir (9). Gschwantler M ve ark., çalışma süresindeki dönemde TIPS hastalarında median trombosit sayısının %19,7 oranında arttığını bulmuşlardır (9). Diğer yandan, Barney EJ ve ark. tarafından yapılan retrospektif çalışmada ise polytetrafluoroethylene (PTFE)-coated TIPS işlemi sonrasında sirotik hastalardaki trombositopenide anlamlı bir iyileşme olmadığının gözlemlenildiği bildirilmiştir (10). Çalışmamızda da dalak uzunluğu ≥18 cm olmasının trombositopeninin daha da derinleşmesi ile ilişkili olduğu görüldü.

Lv YF ve ark. sirotik portal hipertansiyona bağlı hipersplenizmi olan hastalarda yaptıkları çalışmada splenoktemi sonrasında periferal kan hücrelerinde anlamlı artış olduğunu bildirmişlerdir (11). Shah SH ve ark. sirozdaki splenik fagositik aktivitenin dalak büyüklüğü ile birlikte arttığını da göstermişlerdir (12). Shah SH ve ark. dalak hacmi ile lökosit sayısının negatif olarak korele olduğunu da bildirmişlerdir (12). Latorre R ve ark. sirotik hastalarda yaptıkları çalışmada dalak volümü ile trombosit sayısının negative korele olduğunu göstermişlerdir (13). Diğer yandan, Mihaylova-Strashilova M ve Tonchev PT tarafından yapılan çalışmada ise karaciğer sirozu olan hastaların yaklaşık % 12,46'sında trombositopeninin diğer hematolojik anomalilere eşlik etmediği

bildirilmiştir (14). Ek olarak, Latorre R ve ark. hepatic venlerden alınan thrombopoietin düzeyi ile karaciğer fonksiyon testleri bilirubin ve INR (International normalized ratio) değerleri arasında da negatif korelasyon olduğunu da göstermişlerdir (13). Ayrıca, Latorre R ve ark. kompanse sirozlu hastalarda trombosit düzeyi ile periferik venden alınan TPO düzeylerinin arasında pozitif korelasyon olduğunu da göstermişlerdir (13). Çalışmamızda ise, gruplar arası analizde, dalak uzunluğu ≥15 cm olmasının WBC/lenfosit/monosit düzeylerinde istatistiksel olarak anlamlı derecede daha düşük değerler ile ilişkili olduğu gözlendi. Ancak, sadece dalak boyutu >13 cm olan karaciğer sirozu hastalarında çalışmamızda yapılan ayrı bir analizde ise, dalak boyutu arttıkça, WBC, nötrofil, lenfosit, monosit ve platelet değerlerinde azalma olduğu gözlendi. Bu analizlerden, dalak boyutu >13 cm olan karaciğer sirozu hastalarında WBC, nötrofil, lenfosit, monosit ve platelet değerlerinde dalak boyutu artması ile beraber düşüş trendi görülebileceği ama belirgin sitopenik düşüşlerin ise dalak uzunluğu ≥15 cm'den sonra oluşmaya başlayabileceği sonucuna varıldı.

Dalak uzunluğu 15 cm'nin altında olan WBC, nötrofil, lenfosit, trombosit, monosit düşüklüklerinde lökopeni/trombositopeni hemen karaciğer sirozuna bağlanmamalıdır ve ayırıcı tanıya girebilecek diğer etiyolojik faktörler açısından da dikkatli olunmalıdır. Bununla birlikte karaciğer sirozu hastalarında splenomegali arttıkça sitopeniler daha fazla derinleşebileceği ihtimali açısından da sitopenileri ilerleyen karaciğer sirozu hastalarında karşılaştırmalı dalak görüntülemesi de yapılmalıdır.

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Mucize Ağaç: Moringa Oleifera ve Sağlık Üzerine Etkileri

Miracle Tree: Moringa Oleifera and Effects on Health

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ÖZ

Halk arasında "mucize ağaç" olarak adlandırılan *Moringa oleifera* bitkisi, kalsiyum ve potasyum gibi mineralleri, A, C ve E vitamini gibi antioksidan vitaminleri ve polifenoller, fenolik asitler ve flavonoidler gibi biyoaktif bileşikleri içermektedir. Güney Himalayalar, Hindistan, Bangladeş, Afganistan ve Pakistan, Afrika, Amerika ve Asya'nın tropikal ve subtropikal bölgelerinde yetiştirilmektedir. Bazı toplumlar tarafından eski çağlardan itibaren birçok hastalığın tedavisinde iyileştirici etkisi olduğu düşünüldüğü için tüketilmiştir. Özellikle Asya ve Afrika ülkelerinde günümüzde de insan ve hayvan beslenmesi ile birçok rahatsızlığın tedavisi için kullanılmaktadır. *Moringa oleifera'*nın sağlık üzerine olumlu etkileri yüksek biyoaktif molekül içeriği ve elzem amino asitleri içermesi ile açıklanmaktadır. *M. oleifera* yaprakları portakalda bulunandan daha yüksek bir konsantrasyonda C vitamini ve fındıkta bulunana benzer konsantrasyonlarda E vitamini içermektedir. Özellikle yapraklarının içerdiği bazı elzem aminoasitler sayesinde gelişmekte olan ülkelerdeki diyette yetersiz olan proteinin karşılanmasında kullanılabileceği bildirilmektedir Ayrıca içeriğindeki karbonhidratların yaklaşık %20'sinin ise bağırsak sağlığını iyileştirici, antihiperlipidemik ve antihipertansif etkileri olan diyet posasından oluştuğu gösterilmektedir. Bununla birlikte besin ögesi içeriği *M. oleifera*'nın olgunlaşma düzeyi ve yetiştiği bölgeye göre değişiklik gösterebilmektedir. *Moringa oleifera*'nın antioksidan, antiinflamatuar, antibakteriyel, antidiyabetik, antihipertansif özelliklerinin yanında obezite ve kansere karşı da koruyucu etkisi bulunmaktadır. Bu derlemenin amacı, birçok yararlı etkisi olduğu düşünülen *M. oleifera* bitkisini besin ögesi içeriğini ve sağlık üzerindeki etkilerini incelemektir.

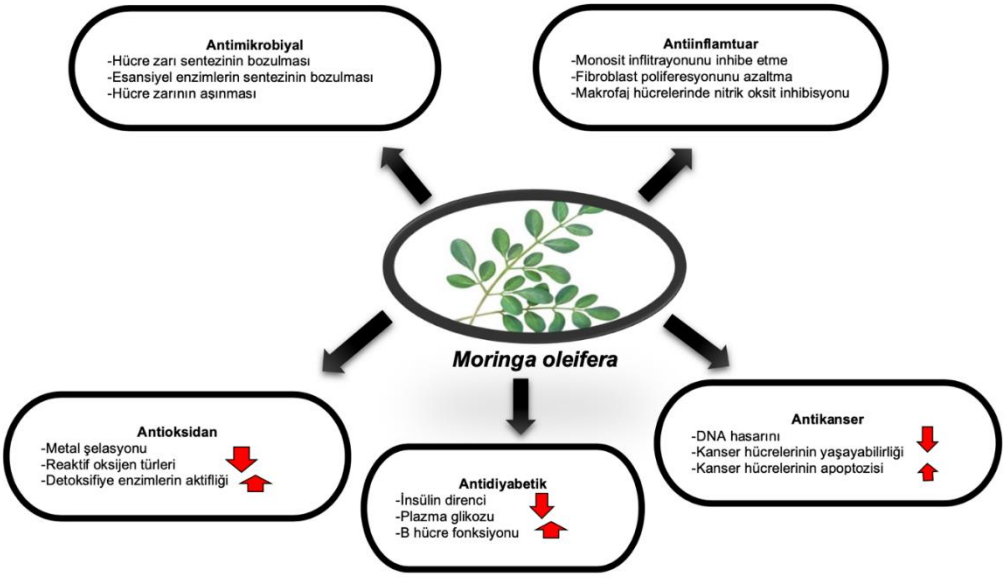
Anahtar Kelimeler: *Antioksidan, Antiinflamatuar, Antimikrobiyal, Moringa oleifera, Polifenoller*

ABSTRACT

The *Moringa oleifera* plant, popular as the "miracle tree", contains minerals such as calcium and potassium, antioxidant vitamins such as vitamins A, C and E, and bioactive compounds such as polyphenols, phenolic acids and flavonoids. It is grown in the tropical and subtropical regions of the Southern Himalayas, India, Bangladesh, Afghanistan and Pakistan, Africa, America and Asia. Some societies have consumed it since ancient times because it is thought to have a healing effect in treating many diseases. It is still used today, especially in Asian and African countries, in human and animal nutrition and for the treatment of many diseases. The positive effects of *Moringa oleifera* on health are explained by its high bioactive molecule content and essential amino acids. *M. oleifera* leaves contain a higher concentration of vitamin C than found in oranges and vitamin E in concentrations similar to those found in hazelnuts. It is reported that it can be used to meet the protein deficiency in developing countries' diets, especially thanks to some essential amino acids contained in its leaves. In addition, it has been shown that approximately 20% of the carbohydrates in its content consist of dietary fiber, which has intestinal health-improving, antihyperlipidemic and antihypertensive effects. However, the nutrient content may vary depending on the maturity level of *M. oleifera* and the region where it is grown. *Moringa oleifera* has antioxidant, anti-inflammatory, antibacterial, antidiabetic and antihypertensive properties as well as a protective effect against obesity and cancer. The purpose of this review is to examine the nutrient content and health effects of the *M. oleifera* plant, which is thought to have many beneficial effects.

Keywords: *Antioxidant, Antiinflammatory, Antimicrobial, Moringa oleifera, Polyphenols*

GRAFİK ÖZET



GİRİŞ

"Mucize ağaç" olarak da bilinen *Moringa oleifera* ağacı, on üç farklı tür içeren tropik çiçekli bitki ailesi Moringaceae familyasına aittir. Güney Himalayalar, Hindistan, Bangladeş, Afganistan ve Pakistan'ın kuzey doğusuna özgü bir ağaç olmakla beraber günümüzde Afrika, Amerika ve Asya'nın tropikal ve subtropikal bölgelerinde de yetiştirilmektedir (1). Boyu 10-12 metreye kadar uzayabilen çok yıllık bir ağaçtır. Farklı toprak, sıcaklık ve yağış koşullarına uyum sağlayabildiği için ekolojik plastisitesi yüksektir. Genellikle besleyici kabukları, yenilebilir yaprakları ve çiçekleri için yetiştirilmekte ayrıca ilaç, kozmetik yağ ve hayvancılıkta yem olarak kullanılmaktadır (2).

Antik çağlarda krallar ve kraliçeler tarafından *M. oleifera'*nın yaprakları ve meyvelerinin zihin ve cilt sağlığını korumak için kullanılmıştır (3). Hindistan'ın eski Maurya savaşçılarının ekstra enerji sağladığı ve savaş sırasında maruz kaldıkları stres ile acıyı hafiflettiğini düşündükleri için cephede Moringa yaprağı özü tükettiği bildirilmektedir. Yetiştirildiği bölgelerin insanları tarafından sağlık üzerine yararlı etkilerinden dolayı yaygın olarak kullanılmakta ve hastalıkları iyileştirici etkisi olduğu düşünüldüğü için "mucize ağaç" olarak adlandırılmaktadır (4).

M. oleifera'nın en çok kullanılan kısmı olan yaprakları çeşitli vitaminler, karotenoidler, polifenoller, fenolik asitler, flavonoidler, alkaloidler, glukozinolatlar, izotiyosiyanatlar, tanenler ve saponinler bakımından zengindir. *M. oleifera*'nın sağlık üzerindeki olumlu etkilerinde içerdiği bu biyoaktif bileşiklerin etkili olduğu düşünülmektedir (5). *M. oleifera* yapraklarının içerdiğindeki biyoaktif bileşenlerin farmakolojik özellikleri çeşitli in vitro ve in vivo çalışmalarda gösterilmiştir (1,6). *M. oleifera*'nın kökleri, kabuğu, yaprağı, meyvesi, çiçekleri ve tohumunun antidiyabetik, hipotansif, antiinflamatuar, antibakteriyel etkileri bulunmakla birlikte bitkinin hepatik ve renal fonksiyonları iyileştirdiği belirtilmiştir (7,8). Ayrıca oksidatif strese (1), kansere (9) karşı koruma sağladığı ve anne sütünü artırıcı (10) etkisi olduğu bildirilmiştir. Bu derlemenin amacı, *Moringa oleifera* bitkisinin sağlık üzerine olan etkilerini incelemektir.

Besin Değeri

Moringa protein, kalsiyum ve potasyum gibi mineraller, C vitamini ve β-karoten gibi antioksidan bileşikler içermektedir. Bu nedenle gelişmekte olan ülkelerde yaşayan yetişkinler ve çocuklarda sık görülen beslenme yetersizliklerini önlemek için besin takviyesi olarak kullanılmaktadır (2,4,8). *M. oleifera*'nın taze yaprak, kuru yaprak, yaprak tozu ve tohumunun 100 gramındaki besin ögesi değerleri Tablo 1'de gösterilmiştir.

Tablo 1: *M. oleifera*'nın Taze Yaprak, Kuru Yaprak, Yaprak Tozu ve Tohumunun 100 Gramındaki Besin Ögesi Değerleri (8,13)

Besin ögesi	Taze yaprak	Kuru yaprak	Yaprak tozu	Tohum
Enerji (kkal)	92	329	205	-
Karbonhidrat (g)	12,5	41,2	38,2	8,67
Protein (g)	6,7	29,4	27,1	2,5
Yağ (g)	1,7	5,2	2,3	38,6
Posa (g)	0,9	12,5	19,2	2,87
Kalsiyum (mg)	440	2185	2003	4,5
Bakır (mg)	0,07	0,49	0,57	5,2
Demir (mg)	0,85	25,6	28,2	-
Magnezyum (mg)	42	448	368	635
Fosfor (mg)	70	252	204	75
Kükürt (mg)	-	-	870	0,05
A vitamini (mg)	1,28	3,63	16,3	-
B_1 vitamini (mg)	0,06	2,02	2,64	0,05
B_2 vitamini (mg)	0,05	21,3	20,5	0,06
B_3 vitamini (mg)	0,8	7,6	8,2	0,2
C vitamini (mg)	220	15,8	17,3	4,5
E vitamini (mg)	448	10,8	113	751,6

M. oleifera'nın yaprak tozu yaklaşık %38,2 oranında karbonhidrat içermektedir. Bunun yaklaşık %20'si ise antihiperlipidemik, bağırsak sağlığını iyileştirici ve antihipertansif özelliklere sahip diyet posasından oluştuğu bildirilmektedir (11). *M. oleifera* 17 çeşit yağ asidi içermekle birlikte α-Linolenik asit %44,6'lık oranla içeriğinde bulunan en yüksek yağ asididir. *M. oleifera*'nın besin ögesi içeriği, olgunlaşma düzeyi ve yetiştiği bölgeye göre değişiklik gösterebilmektedir (12).

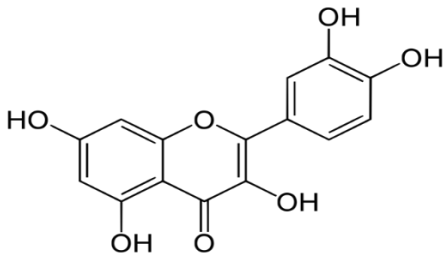
M. oleifera yaprakları diğer bitki yapraklarıyla kıyaslandığında daha yüksek miktarda protein içerdiği görülmektedir. Kurutulmuş yaprakların yaklaşık %30'u ham protein ve 19 amino aside sahiptir (12). *M. oleifera* tereonin, lösin, fenilalanin, triptofan gibi çeşitli elzem amino asitler içerir (8). *M. oleifera*'nın taze yaprak, kuru yaprak ve yaprak tozunun 100 gramındaki elzem amino asit miktarları Tablo 2'de gösterilmiştir.

Tablo 2: *M. oleifera*'nın Taze Yaprak, Kuru Yaprak ve Yaprak Tozunun 100 Gramındaki Elzem Amino Asit Miktarları (8)

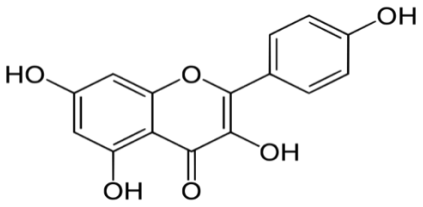
Amino asit	Taze yaprak	Kuru yaprak	Yaprak tozu
Arjinin (g/16 gN)	%6	%1,78	%1,33
Histidin (g/16 gN)	%2,1	%0,716	%0,61
Lizin (g/16 gN)	%4,3	%1,637	%1,32
Triptofan (g/16 gN)	%1,9	%0,486	%0,43
Fenilalanin (g/16 gN)	%6,4	%1,64	%1,39
Metionin (g/16 gN)	%2	%0,297	%0,35
Teronin (g/16 gN)	%4,9	%1,357	%1,19
Löysin (g/16 gN)	%9,3	%1,96	%1,95
İzolöysin (g/16 gN)	%6,3	%1,177	%0,83
Valin (g/16 gN)	%7,1	%1,413	%1,06

Biyoaktif Bileşenleri

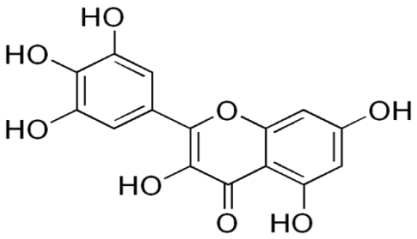
M. oleifera polifenoller, saponinler, tanenler, alkaloidler gibi çeşitli biyoaktif bileşikleri içeren önemli bir bitkidir. *M. oleifera* yaprağında alkaloidler, tanenler, saponinler, izotiyosiyanat ve glukosinolat gibi biyoaktif bileşenler saptanmıştır. Yapraklarında bulunan ana fenolik bileşikler kaempferol, mirisetin, quarsetin, klorojenik asit, gallik asit, luteolin, vanilin ve rutindir (14) (Şekil 1). *M. oleifera*'nın antioksidan, antiinflamauar, antimikrobiyal gibi sağlık üzerine yararlı etkilerinin bu biyoaktif bileşenlerden kaynaklandığı düşünülmektedir (1,6).



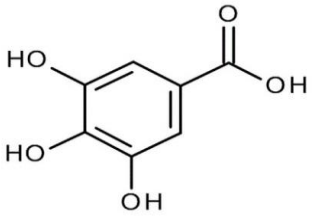
Quarsetin



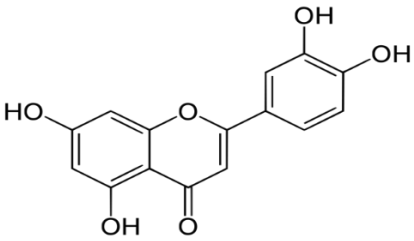
Kaempferol



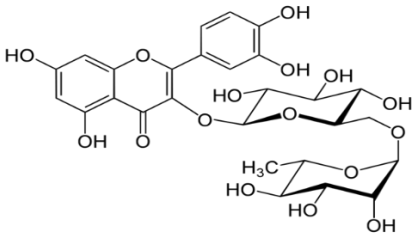
Mirisetin



Gallik asit



Luteolin



Rutin

Şekil 1: *Moringa Oleifera* Yapraklarındaki Bazı Fenolik Bileşiklerin Kimyasal Yapısı (6)

Vitaminler

M. oleifera'nın taze yaprakları iyi bir A, C ve E vitamini kaynağıdır. Bitki, bu antioksidan vitamin içeriğine bağlı olarak vücudu serbest radikallere karşı korumaktadır. *M. oleifera* yaprakları ayrıca portakalda bulunandan daha yüksek bir konsantrasyonda C vitamini (200 mg/100 g) ve fındıkta bulunana benzer konsantrasyonlarda E vitamini (10,8 mg/100 g) içermektedir (15). *M. oleifera*'nın yetişkin yapraklarında 5,7 µg/g ile 27,8 µg/g kuru kütle arasında değişen yüksek bir γ-tokoferol içeriği bulunmuştur. α-tokoferol değeri ise 95,9 µg/g ile 744,5 µg/g arasında değiştiği bildirilmiştir. α-tokoferol değerindeki bu önemli farklılıklar bitkilerin yaşı ve çeşitli kısımları arasındaki farklılıkla açıklanmaktadır (16).

M. oleifera yaprakları pro-vitamin A potansiyeline sahip iyi bir karotenoid kaynağıdır (15). *M. oleifera*'da başta β-karoten (401 mg/kg kuru madde) olmak üzere çeşitli ksantinler (neoxanthin 219 mg/kg, violaxanthin 76,5 mg/kg, zeaksantin 19,4 mg/kg) içermektedir. Ayrıca Hindistan ve Filipinler'de antioksidan vitamin içeriğiyle ilişkili olarak besinleri korumak için taze *M. oleifera* yaprakları kullanılmaktadır (16).

Polifenoller

M. oleifera'nın yaprakları flavonoidler ve fenolik asitler gibi polifenol bileşiklerini içermektedir (8,17). Yapraklarda bulunan başlıca fenolik bileşikler; liganlar, flavonoidler, fenolik asitler ve bunların türevleridir. *M. oleifera* yapraklarında bulunan ana flavonoidler sırasıyla 5,8, 0,207 ve 7,57 mg/g konsantrasyonlarda mirisitin, quarsetin ve kaempferoldur (18). *M. oleifera* yapraklarının metabolik ekstraktındaki toplam fenolik içerik 71,08±12,05 ile 76,63±10,63 mg GAE/g arasında değişmektedir (19).

Alkoloidler, glukosinotlar ve izotiyosinatlar

N, α-L-ramnopiranosilvinkozamid, fenilasetonitrilpirolemerumin, 40-hidroksifeniletanamid- α-L-ramnopiranosid ve bunun glukopiranosil türevi, *M. oleifera* yapraklarında bulunan başlıca alkaloidlerdir (20). Bu alkaloidler ve türevlerinin antibakteriyel, antiinflamatuar, antitümör, hipotansif gibi etkileri nedeniyle yaygın olarak kullanılmaktadır. Glukosinolatlar, yapraklarda ve tohumlarda bulunan ve 4-O-(a-L-rhamnopiranosiloksi)-benzilglukozinolatın (glukomoringin) başlıca olduğu başka bir tür ikincil metabolittir (21,22). Tohumların glukosinolatlar açısından zengin olduğu ve içeriğin yapraklara ve diğer kısımlara göre çok daha yüksek olduğu bulunmuştur. Glukomoringin *M. oleifera*'da en çok bulunan glukosinolatlardır (13).

Tanenler

Tanenler, proteinleri, alkaloidleri ve diğer organik molekülleri çökelten suda çözünür polifenolik büzücü biyomoleküllerdir. *M. oleifera*'nın kuru yapraklarda 13,2 ile 20,6 g tanen/kg arasında değişen konsantrasyonlarda tanen içeriğine sahiptir (23).

Saponinler

Saponinler, şeker parçalarına kovalent olarak bağlı izoprenoid türevi aglikondan oluşan *M. oleifera* yapraklarındaki diğer organik bileşiklerdir. Dondurularak kurutulmuş yaprak içeriği 64 ile 81 g/kg kuru ağırlık arasında değişmektedir (24).

Sağlık Üzerine Etkileri

M. oleifera yaprakları antioksidan aktivite, antimikrobiyal aktivite, antikanserojen etki ve antiinflamatuar etki gibi çok sayıda özelliğe sahiptir. Özellikle Asya ve Afrika ülkelerinde insan ve hayvan beslenmesi ve birçok rahatsızlığın tedavisi için tüketilmektedir (14). Stevens ve ark. (25) *M. oleifera*'nın Nijerya'da kullanımı ile ilgili yaptıkları çalışmada yaprakların tıbbi kullanımları arasında ateşin düşürülmesi (%78,7), kulak enfeksiyonlarının tedavisi (%71,8), kan şekerini (%65,2) ve kan basıncını (%64,7) düşürmenin yer aldığını belirtmişlerdir. Bu sağlık üzerine yararlı etkilerinden çok çeşitli alkaloid ve sterol, polifenoller ve fenolik asitler, yağ asitleri, flavanoidler ve flavanol glikozitler, glukozinolat ve izotiyosiyanat, terpen, antosiyaninler vb.'nin sorumlu olduğu düşünülmektedir (26). Özellikle son yıllarda hızla artan genetik, çevresel ve sağlıksız yaşam tarzı faktörlerinin neden olduğu bulaşıcı olmayan hastalıkların önlenmesi ve kontrolü önemli hale gelmektedir. *M. oleifera* içerdiği besin ögeleri ve çeşitli bileşenleri aracılığıyla normal hücre DNA'sının hasar görmesini önleme ve kanser hücresi apoptozisini teşvik etme gibi etkileriyle kronik hastalıkların önlenmesinde etkili olabileceği düşünülmektedir (27). Toksisitesi düşük olan *M. oleifera*'nın yaygın olarak kullanılan konsantrasyonları çok az yan etkiye neden olabilmektedir. Yaprakların bildirilen LD50 değeri 1585 mg/kg'dır. Wistar sıçanına 6400 mg/kg'a kadar dozlarda oral yoldan verilen *M. oleifera* yapraklarının sulu özütü herhangi bir ölüme neden olmamıştır ancak yüksek doz sıçanlarda azalmış ve donuk hareket kabiliyetini tetiklemiştir (13).

Antioksidan etkisi

M. oleifera yüksek antioksidan içeriği ile bilinmektedir ve yaklaşık 40 doğal antioksidan içermektedir. Antioksidan aktivite, askorbik asit, β-karoten, tokoferoller, flavonoidler, fenolikler, izotiyosiyanatlar gibi çeşitli tipte antioksidan bileşiklerin varlığına atfedilmektedir (26). Yaprak ekstraktının uygulanması, bireylerde hipoglisemi etkisi olmadan plazma malondialdehit (MDA) seviyesini ve plazmanın ferrik indirgeme kabiliyetini korumuştur (28). Diyabetik fareler üzerine

yapılan bir çalışmada *M. oleifera* kabuklarının metanolik özü ile tedavi ettikten sonra, süperoksit dismutaz (SOD), glutatyon (GSH) aktivitelerinin olduğu gösterilmiştir (29). Ayrıca DPPH, $ABTS^{+}$, CPZ^{+}, O_2, H_2O_2 vb. gibi serbest radikalleri güçlü bir şekilde süpürme yeteneğine sahip olduğu kanıtlanmıştır ve HL-60 hücresinde antioksidan aktivitesi doğrulanmıştır (30).

Antiinflamauar etkisi

M. oleifera'nın yaprak, meyve, tohum ve kök ekstraktları astım, alerjik rinit, atopik dermatit ve romatoid artrit gibi inflamasyonla ilişkili bozuklukların iyileştirilmesinde çok eskiden beri kullanılmaktadır (31). Antiinflamatuar aktivite içeriğinde bulunan izotiyosiyanat, quercetin, kaempferol gibi fenolik bileşiklerle ilişkilendirilmektedir (26). Saleem ve ark. (32) romatoid artrit modeli oluşturdukları farelerde *M. oleifera*'nın metanolik ekstraktının C-reaktif protein, prostaglandin E2 ve TNF-α'nın serum konsantrasyonunu önemli ölçüde azalttığını; IL-1β ve I-κB, IL4 ve IL-10'un mRNA seviyelerini önemli ölçüde yukarı regüle ettiğini ve eklemlerdeki histopatolojik indeksleri ve artritik indeksi önemli ölçüde onardığını göstermişlerdir. *M. oleifera*'nın bağışıklıkla ilgili çoklu etkilerini, öncelikle patojenleri doğrudan ortadan kaldırarak veya NF-κB yolu gibi sinyal yollarının aktivitesini düzenleyerek çeşitli bağışıklık hücrelerinden salınan pro ve antiinflamatuar aracıların dengesini modüle ederek gösterdiği belirtilmektedir. *M. oleifera* tohumlarının ve yapraklarının özünün de antiinflamatuar aktivite gösterdiği bildirilmiştir. Yaprağın etil asetat özü diyabetik farelerde TNF-α, IL-6 ve IL-1β'yi azalttığı, ROS ve hiperglisemiden kaynaklanan hasarı önlediği gösterilmiştir (33).

Antimikrobiyal etkisi

Antimikrobiyal özelliklerinin yapısındaki kaempferol, rhamnetin, kaempferitin, isoquercitrin gibi bazı biyoaktif moleküller tarafından sağlandığı düşünülmektedir (34). *M. oleifera*'dan ekstrakte edilen doğal bir flavonoid olan kaempferol, bakteri hücre zarının bütünlüğünü bozarak doza bağlı antimikrobiyal etki gösterdiği bildirilmiştir (3). *M. oleifera*'nın çeşitli bölgelerinden elde edilen farklı özlerin hem gram negatif hem de gram pozitif bakterilere karşı antibakteriyel özellikler gösterdiği bildirilmiştir (26). Yapılan çalışmalarda, *M. oleifera*'nın *E. coli, Enterobacter aerogenes, Klebsiella pneumonia, P. aeruginosa* ve *Providencia stuartii* (35); *V. cholera, V. vulnificus* ve *V. mimicus*'a (36); *S. aureus, P. aeruginos*'ya (37) karşı etkili olduğu; *T. mentagrophyte, Pullarium* spp., *A. flavus, Penicillium* spp., *A. niger, A. oryzae, A. terreus* ve *C. Albicans*'a karşı önemli antifungal aktivite sergilediği gösterilmiştir (26). Bitkinin nispeten geniş bir anti-mikrobiyal spektruma sahip olduğu gösterilmekle beraber gram negatif bakterilere karşı biraz daha yüksek inhibitör etki gösterdiği, özellikle yapraklar ve tohumunun, diğer kısımlarına göre daha geniş bir anti-mikrobiyal aktivite spektrumuna sahip olduğu belirtilmektedir (3). *M. oleifera*'da bulunan bazı amino asitler, metal iyonları ile etkileşime girebilmekte, bu şekilde patojenlerin etkisiz hale gelmesini sağlayan negatif yüklü bir ortam oluşturmaktadır. *M. oleifera*'da bulunan moringa pıhtılaştırıcı proteinlerinin kirli suyu arıtma, asit-baz dengesini düzenleme ve antiseptik etkisi vardır. Pıhtılaştırıcı proteinler, absorpsiyon ve nötrleştirme işlevleri aracılığıyla mikroorganizmaları topaklaştırabilir ve etkisiz hale gelmesini sağlar (38).

Hipolipidemik etkisi

Hiperlipidemi, kardiyovasküler hastalık riskini artıran bir durumdur. *M. oleifera*'daki birçok biyoaktif bileşen lipit homeostazının korunmasına katkıda bulunabilmektedir. *M. oleifera*'nın yaprak tozu ve hidroalkolik ekstraktının hiperkolesteremik sıçanlarda vücut ağırlığını, serum total kolesterol, trigliserit, VLDL ve LDL düzeylerini azaltabileceği ve serum HDL düzeylerini artırabileceği bildirilmiştir (39). Yapılan başka bir çalışmada da *M. oleifera*'nın AMPK sinyal yolunu aktive ederek lipogenezi inhibe ettiğini gösterilmiştir (40).

Antidiyabetik etkisi

Diyabet ciddi komplikasyonları olan yüksek kan şekeri seviyeleri ile karakterize edilen kronik metabolik bir hastalıktır. Sağlıklı beslenme, düzenli fiziksel aktivite ve normal vücut ağırlığını koruma tip 2 diyabeti önlemede önemli faktörlerdendir (41). *M. oleifera*'nın antidiyabetik etkiler

gösterdiği bildirilmiştir. *M. oleifera*'nın bu etkisinin pankreasın ß hücrelerinin uyarılmasında rol oynayan ve bunun sonucunda insülinin salınmasını sağlayan terpenoidlerin ve flavonoidlerin varlığından kaynaklanabileceği belirtilmektedir. Ayrıca içerdiği glucomoringin (glukosinolatlar), kuersetin ve kaempferol (flavonoidler) ve asklorojenik asit gibi bileşenlerin hipoglisemik özellikleri olduğu göstermiştir (26). Leone ve ark. (42)'nın yürüttüğü bir çalışmada 20 g/gün *M. oleifera* yaprağı tozunun bireylerde postprandiyal glisemik yanıtta bir azalma sağladığı gösterilmiştir. *M. oleifera* kapsüllerinin, plazmadaki insülin konsantrasyonunu iyileştirebileceği ve PKA sinyal yolu yoluyla insülin salgılanmasını kolaylaştırarak diyabetik sıçanlarda ß hücresinin işlevini artırabileceği gösterilmiştir (43).

Hipotansif etkisi

Hipertansiyon inme, koroner arter hastalığı ve kalp yetmezliği gibi diğer kardiyovasküler hastalıkların riskini artıran bir hastalıktır. Periferik vasküler direnç, kan basıncının bir belirleyicisidir ve özellikle arteriyollerde olmak üzere vasküler düz kasın kasılma durumu tarafından belirlenmektedir (44). *M. oleifera*'da bulunan niazinin, niazimisin, niaziminin, niazimin, niazirin, niazicin, niazirinin gibi çeşitli yaprak bileşenlerinin hipotansif ve bradikardiyak aktivitelerden sorumlu olduğu bildirilmiştir (26). Bitkinin tohum ve yaprak özlerinin içerdiği alkaloidler ve flavonoidler sayesinde, anjiyotensin dönüştürücü enzimler üzerindeki inhibitör etki yoluyla kan basıncını düşürücü etkiye sahip olduğu belirtilmektedir (45). Deneysel bir hipertansif model oluşturulmuş erkek Wistar sıçanlarına 3 hafta süreyle oral olarak uygulanan tedavinin (30 ve 60 mg/kg/gün) yüksek kan basıncını ve taşikardiyi doza bağımlı bir şekilde azaltabileceği gösterilmiştir (46).

Antikanser etkisi

Kanser, apoptozdan kaçma, sınırsız replikasyon potansiyeli, doku metastazı ve nihayetinde habis tümör oluşumuna yol açan diğer genom kararsızlığıyla ilişkili hücre fizyolojisi özellikleri gibi çok sayıda uzaysal-zamansal değişikliğe sahip karmaşık bir hastalıktır (47). *M. oleifera*'nın kanser hücrelerinin gelişimini baskılayarak antineoproliferatif aracı olarak kullanılabileceği kanıtlanmıştır. Yaprak ekstresinin kemoprotektif, sitotoksik, antihepatokarsinom, antilösemi, antimiyelomik ve çoğalmayı önleyici faaliyetler gösterdiği belirtilmektedir (26). Tayland'dan toplanan *M. oleifera* yapraklarının bir özütünün kolon hücrelerinde antiproliferatif aktivite gösterdiği; bu durumunun da kanser ilerlemesi ve metastaz ile yakından ilişkili olduğu bildirilmiştir (48). Adebayo ve ark. (49) tarafından yürütülen bir çalışmada meme kanserli hücrelerde *M. oleifera* tohumlarının ham etanol ekstraktının antiproliferatif etkiler gösterdiği saptanmıştır (IC50 = 130 µg/mL). Olgunlaşmamış *M. oleifera* baklalarının yaklaşık %46,8 posa içerdiği ve *M. oleifera* baklalarının yüksek posa içeriğinden dolayı kolon kanserine karşı koruyucu özellik gösterdiği belirtilmektedir (13).

Antiobezite etkisi

M. oleifera'nın anti-obezite etkisi, hipolipidemik, antioksidan ve antiinflamatuar kapasitesi ile ilişkili olabileceği bildirilmiştir (8). Ayrıca yapraklarının enerji içeriğinin düşük olmasından dolayı obez bireylerin beslenmesinde kullanılabileceği belirtilmektedir (13).

SONUÇ ve ÖNERİLER

Moringa oleifera esansiyel amino asitler, vitaminler, mineraller gibi diyet bileşenlerinin bir kaynağı olan bir bitkidir. Özellikle bitkinin en çok kullanılan kısmı olan yaprakları çeşitli vitaminler, karotenoidler, polifenoller, fenolik asitler, flavonoidler, alkaloidler, glukozinolatlar, izotiyosiyanatlar, tanenler ve saponinler açısından zengindir. *Moringa oleifera* yapraklarına atfedilen olumlu farmakolojik özellikleri yapraklarının yüksek biyoaktif molekül içeriği ile açıklanmaktadır. İçeriğindeki biyoaktif moleküller önemli bir serbest radikal temizleme etkisine sahiptir. Antioksidan özelliği ile beraber antimikrobiyal aktivite ve antiinflamatuar etki gibi özelliklere sahiptir Özellikle son yıllarda hızla artan genetik, çevresel ve sağlıksız yaşam tarzı faktörlerinin neden olduğu kronik hastalıkların önlenmesinde etkili olabileceği düşünülmektedir. DNA hasarı azaltıp kanser hücrelerinin apoptozisini artırarak antikanserojen etki de göstermektedir.

Diyabetin tedavisinde pankreasın ß hücrelerinin uyarılmasında rol oynayarak insülinin salınmasını sağlayabileceği gösterilmiştir. Posa içeriğinin yüksek olması nedeni ile de antihiperlipidemik ve antihipertansif etkilerinin olduğu ve bağırsak sağlığını olumlu etkilediği bildirilmiştir. Bununla birlikte içerdiği elzem amino asitler sayesinde yetersiz beslenmenin sık görüldüğü gelişmekte olan ülkelerde beslenme yetersizliklerinin önlenmesinde kullanılabilir. Ayrıca enerji içeriğinin düşük olması nedeniyle obez bireylerin beslenmesinde de kullanılabilir.

In vitro ve deney hayvanları ile yapılan birçok çalışmada *M. oleifera*'nın çok sayıda olumlu farmakolojik özelliği geniş çapta incelenmiş ve doğrulanmıştır. *M. oleifera*'nın, sağlıklı beslenmenin yanı sıra birçok hastalığın tedavisi ve önlenmesinde ucuz ve güvenilir bir alternatif olabileceği belirtilmektedir. *M. oleifera*'nın yaygın olarak kullanılan konsantrasyonları çok az yan etkiye neden olduğu ve toksisitesinin düşük olduğu gösterilmiştir. Bunun yanı sıra, insanlar üzerindeki etkilerine dair kanıtlar yetersizdir. *M. oleifera*'nın insanlar üzerindeki farmakolojik etkilerini araştırmayı ve aynı zamanda uzun süreli kullanımının insan sağlığı üzerindeki güvenilirliğini belirlemeyi amaçlayan ileri çalışmalara ihtiyaç vardır.

Çıkar çatışması: Yazarlar çıkar çatışması olmadığını beyan ederler.

Yazarlık katkısı: Makalenin tasarımı: ŞNE, KT; Makale verilerinin elde edilmesi: ŞNE; Verilerin analiz edilmesi: ŞNE; Makale taslağının oluşturulması: ŞNE; İçerik için eleştirel gözden geçirme: KT; Yayınlanacak versiyonun son onayı: KT.

Maddi destek: Yazarlar maddi destek almadıklarını beyan ederler.

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