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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Tek Merkez Deneyimi: Feokromasitoma Olgularının Retrospektif Değerlendirilmesi

Single Center Experience: Retrospective Evaluation of Pheochromocytoma Cases

Murat Çalapkulu[1], Muhammed Erkam Sencar[1], İlknur Öztürk Ünsal[1], Davut Sakız[2], Mustafa Özbek[1], Erman Çakal[1]

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ABSTRACT

Aim: *Pheochromocytomas are neuroendocrine tumors originating from chromaffin cells. The aim of the current study is to review the clinical, laboratory, and imaging findings of pheochromocytoma.*

Material and Method: *Clinical, laboratory, and radiological data of a total of 19 patients diagnosed with pheochromocytoma between 2009–2019 were evaluated retrospectively.*

Results: *Of the 19 patients diagnosed with pheochromocytoma, 13 were female, and 6 were male, and the mean age of 44.1±11.3 years. Hypertension was present in 18 patients, of which 8 were newly diagnosed. It was found that thyroid pathologies were most common after hypertension in patients with pheochromocytoma. The most common symptom after high blood pressure was sweating and headache. All patients had vitamin D deficiency or insufficiency. In 94.1% of patients, the level of normetanephrine observed was found to be elevated. 11 were right-sided, 5 were left-sided, and the remaining 3 were bilateral. The lesion size was less than 4 cm in 36.8%, between 4–6 cm in 42.1%, and greater than 6 cm in 21.1%.*

Conclusion: *In the current study showed that pheochromocytoma has a nonspecific and variable clinic feature. In patients with suspected pheochromocytoma, 24-hour urine normetanephrine and metanephrine levels should be requested as a screening test, especially during attacks, and surgical treatment should be performed after the mass is localized with imaging methods.*

Key words: *pheochromocytoma; hypertension; catecholamine; symptoms; diagnosis; vitamin D*

ÖZET

Amaç: *Feokromositomalar kromaffin hücrelerinden kaynaklanan nöroendokrin tümörlerdir. Bu çalışmanın amacı feokromasitoma hastalarının klinik, laboratuvar ve görüntüleme bulgularını gözden geçirmektir.*

Materyal ve Metot: *Araştırmamızda 2009–2019 yılları arasında feokromasitoma tanısı almış 19 olguya ait klinik, laboratuvar ve radyolojik veriler geriye dönük olarak değerlendirilmiştir.*

Bulgular: *Feokromasitoma tanısı konan 19 hastadan 13'ü kadın, 6'sı erkek olup ortalama yaş 44,1±11,3 yıl olarak saptandı. Hastaların 8 tanesi yeni tanı olmak üzere 18'inde hipertansiyon mevcuttu. Feokromositoma hastalarına eşlik eden hastalıklar incelendiğinde, hipertansiyondan sonra en sık tiroid patolojilerinin olduğu bulundu. Tansiyon yüksekliğinden sonra en sık semptom terleme ve baş ağrısı olarak saptandı. Tüm hastalarda vitamin D eksikliği ya da yetersizliği mevcuttu. Hastaların %94,1'inde 24 saatlik idrarda bakılan normetanefrin düzeyi yüksek olarak saptandı. Yerleşim yerleri açısından on birinde sağda, beşinde solda ve üçünde tümör bilateral adrenal yerleşimliydi. Lezyon boyutu %36,8'inde 4 cm'den küçük, %42,1'inde 4–6 cm arasında saptanırken, %21,1'inde 6 cm'den büyük saptandı.*

Sonuç: *Bu çalışma feokromasitomanın nonspesifik ve değişken bir kliniğinin olduğunu gösterdi. Feokromasitoma şüphesi olan hastalarda özellikle ataklar sırasında tarama testi olarak 24 saatlik idrarda normetanefrin ve metanefrin düzeyleri istenmeli ve görüntüleme yöntemleri ile kitle lokalize edildikten sonra cerrahi tedavi uygulanmalıdır.*

Anahtar kelimeler: *feokromasitoma; hipertansiyon; katekolamin; semptomlar; tanı; vitamin D*

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Giriş

Adrenal medullanın katekolamin sekrete eden kromaffin hücrelerinden kaynaklanan tümörlere feokromasitoma, adrenal dışında yerleşen sempatik ve parasempatik zincirin kromaffin hücrelerinden köken alan tümörlere ise paraganglioma (ekstra-adrenal feokromasitoma) adı verilmektedir[1,2]. Normal toplumda görülme insidansı 0,8/100000'dir ve hipertansiyonu olan hastaların %0,1–0,6'sında gözlenir[2–5]. Her ne kadar her yaşta ortaya çıkabilirse de, en çok dördüncü ila beşinci dekadda görülür[6]. Erkek ve kadın cinsiyeti eşit sıklıkta etkiler[6]. Tümörlerin yaklaşık %95'i intraabdominal, %85–90'ı adrenal bez içi yerleşimlidir ve %5–10'u birden çok sayıdadır. Ayrıca %10–15'i adrenal bez dışında yerleşimlidir[2]. Tümörlerin çoğu sporadiktir ve malignite sıklıkları %10'dan azdır[2]. Von Hippel-Lindau, nörofibromatozis, multipl endokrin neoplazi (MEN) 2A ve MEN 2B gibi ailesel hastalıklarla birlikte görülebilir[7].

Salgıladığı başlıca hormonlar; norepinefrin, epinefrin, dopamin ve metabolitleridir. Bununla birlikte adrenomedullin, somatostatin, vasopressin, eritropoetin, substance P, beta-endorfin, vazoaktif intestinal polipeptid, adrenokortikotropin, interlökin 6, nöropeptid Y, parathormon related peptid ve kalsitonin gibi değişik hormonlar salgılayabildikleri de gösterilmiştir[8]. Klinik tablo, salgılanan hormonun özelliklerine, çeşitliliğine ve bireylerin katekolamin duyarlılığındaki farklılıklara bağlı olarak değişiklik gösterebilir. En sık başvuru sebepleri hipertansiyon eşliğinde çarpıntı, baş ağrısı ve terleme epizotlarıdır. Daha nadir olarak baş dönmesi, nefes darlığı, karın ağrısı, bulantı, tremor, parestezi gözlenebilir[1,2].

Tanıda, özellikle kriz sırasında bakılan plazma katekolamin düzeyleri ve bu sırada toplanmaya başlanan idrar örneklerinde katekolamin ve/veya metabolitlerinin arttığının gösterilmesi değerlidir[2,8–10]. Feokromositoma varlığı biyokimyasal olarak kanıtlandıktan sonra lokalizasyon amaçlı en sık bilgisayarlı tomografi (BT) ve manyetik rezonans (MR) görüntüleme kullanılır. Lokalizasyon yapılamadığında, pozitron emisyon sintigrafisi (PET) ve metiliyodobenzilguanidin (MIBG) sintigrafisi gibi ileri tetkikler kullanılabilir. Temel tedavi tümörün cerrahi olarak rezeksiyonudur[2,8].

Bu çalışmada kliniğimizde feokromasitoma ile takip edilen hastaların kliniği, tanısı ve tedavisi ile ilgili 10 yıllık deneyimlerimizi literatür eşliğinde tartışmayı amaçladık.

Materyal ve Metot

Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Endokrinoloji ve Metabolizma Kliniği'ne 2009–2019 yılları arasında başvuran ve tetkikleri sırasında feokromasitoma saptanan 19 vakaya ait veriler retrospektif olarak değerlendirildi. Feokromasitoma tanısı; tipik klinik semptomları olan olgularda 24 saatlik idrar katekolamin ve/veya katekolamin metabolitlerinin artmış düzeyleri, görüntülemelerde kitle varlığının saptanması ve cerrahi sonrası elde edilen patolojik inceleme sonuçları ile konuldu. Hastaların kan basınçları Türk Hipertansiyon Uzlaşı Raporu'na göre değerlendirildi[11]. On sekiz yaş üzerindeki erişkinlerde hekim tarafından yapılan, tekrarlanan klinik ölçümler ile sistolik kan basıncının ≥140 mmHg ve/veya diyastolik kan basıncının ≥90 mmHg olması hipertansiyon olarak tanımlandı. Yirmi dört saatlik idrar katekolaminleri yüksek performanslı sıvı kromatografisi (HPLC) yöntemi kullanılarak ölçüldü. Lokalizasyon amaçlı ultrasonografi (USG), BT ve MR görüntülemesi kullanıldı. Bir hastada ise lokalizasyon belirlenmesi amacıyla MIBG sintigrafisi kullanıldı. Ekstraadrenal feokromasitomalar ve inceleme sırasında yeterli veri elde edilemeyen olgular çalışma dışı bırakıldı. Hastaların başvuru semptomları, komorbid durumları, kullandığı antihipertansif ilaçlar, laboratuvar bulguları, radyolojik bulguları ve patolojik bulguları analiz edildi. Bu çalışma için hastalardan bilgilendirilmiş onam ve klinik araştırmalar etik kurulu onayı alındı (09.12.2019, Karar No: 77/01).

İstatistiksel Yöntemler

İstatistiksel analizler SPSS yazılımı (versiyon 21.0, SPSS, Chicago, IL) kullanılarak yapıldı. Kategorik veriler sıklık ve yüzde (%) ile özetlendi. Normal dağılıma sahip devamlı değişkenler ortalama ± standart sapma (SD) değerler olarak, normal dağılıma sahip olmayan değişkenler median (min-max) değerler olarak ifade edildi. Başvuru semptomları, kullanılan antihipertansif ilaçlar, komorbid durumlar gibi kategorik veriler yüzde oranlarıyla birlikte tablolar halinde sunuldu.

Bulgular

Çalışmamıza ortalama yaşları 44,1±11,3 yıl olan 13 kadın (%68,4) ve 6 erkek (%31,6) olmak üzere toplam 19 hasta dahil edildi. Kadın hastaların ortalama yaşları 44,6±12,1 yıl iken, erkek hastaların ortalama yaşları 43±10,1 yıl idi. Hastaların sekizi yeni tanı olmak üzere on sekizinde (%94,7) hipertansiyon mevcuttu. Hipertansiyon tanısı daha önce konulan 10 hastanın

üçünde tansiyon yüksekliği paroksismal iken yedisinde sürekliydi ve bu hastaların hepsi düzenli antihipertansif ilaç kullanıyorlardı. Medyan hipertansiyon süresi 7 (1–25) yıl olarak saptandı. Hastaların sekizi (%42,1) anjiotensin dönüştürücü enzim inhibitörü/anjiyotensin reseptör blokerleri kullanırken, dört (%21,1) hasta üç veya daha fazla sayıda antihipertansif ilaç kullanıyordu. Hipertansiyon tanısı yeni konulan sekiz hasta antihipertansif tedavi almıyordu ve bu hastaların beşinde ataklar şeklinde olan hipertansiyon mevcuttu. Feokromasitomaya eşlik eden komorbid hastalıklar Tablo 1'de verildi. Feokromasitoma hastalarına en sık eşlik eden hastalıklar değerlendirildiğinde ilk sırada hipertansiyon (n: 18 %94,7), ikinci sırada tiroid patolojileri olduğu görüldü (n: 9, %47,4). En sık görülen tiroid patolojisinin tiroid nodülü olduğu saptandı. Üçüncü en sık eşlik eden hastalık tip 2 diyabet olarak saptandı (n: 7, %36,8). Hastaların başvuru semptomlarına ait veriler Tablo 2'de özetlendi. Başvuru esnasında en sık başvuru şikâyetinin kontrol altına alınamayan tansiyon yüksekliği olduğu görüldü (n: 18, %94,7). Bu şikayete terleme, baş ağrısı ve çarpıntı şikayetlerinin eşlik ettiği saptandı. Hastaların laboratuvar parametreleri, 24 saatlik idrarda ölçülen hormon ve metabolit değerleri Tablo 3 ve Tablo 4'de özetlenmiştir. Hastaların biri hariç hepsinde 1 mg deksametazon supresyon testi (DST) baskılı saptandı. Test sonrasında kortizol değeri 3 µg/dl gelen hastaya iki gün 2 mg DST testi yapıldı ve test sonucunda kortizol baskılandı. Tüm hastalarda plazma aldosteron/plazma renin aktivitesi oranı 15'in altında olarak saptandı. Median 25 (OH) D düzeyi 13 µg/L olarak saptandı. Tüm hastalarda vitamin D eksikliği ya da yetersizliği mevcuttu. Tüm hastalarda idrar katekolamin düzeyleri yüksek olarak saptandı. Hastaların %94,1'inde 24 saatlik idrarda bakılan normetanefrin düzeyi yüksek olarak saptandı. Normetanefrin düzeyi normal olan bir hastada metanefrin ve dopamin düzeyi yüksek olarak saptandı. İkinci sırada yüksek olan metabolitin vanilmandelik asit (%70) olduğu görüldü. Hastaların radyolojik ve patolojik bulguları Tablo 5'te görülmektedir. Lezyon hastaların %10,5'inde USG, %31,5'inde BT, %52,6'sında MR ve %5,3'ünde MIBG sintigrafisi ile lokalize edildi. Hastaların %57,9'unda lezyon sağ adrenal bezde, %26,3'ünde sol adrenal bezde, %15,8'inde ise bilateral olarak saptandı. Lezyon boyutu %36,8'inde 4 cm'den küçük, 42,1'inde 4–6 cm arasında saptanırken, %21,1'inde 6 cm'den büyük saptandı. Median Ki 67 düzeyi %1 (1–5) olarak saptandı. Bilateral feokromositoma saptanan, 45 yaşın altında feokromasitoma tanısı alan veya medüller tiroid

Tablo 1. *Eşlik eden hastalıkların dağılımı*

Eşlik eden hastalıklar	Sayı (n)	Hasta yüzde (%)
Hipertansiyon	18	94,7
Tiroid patolojisi	9	47,4
– Tiroid nodülü	5	26,3
– Hipertiroidi	1	5,3
– Hipotiroidi	2	10,5
– Medüller tiroid kanseri	1	5,3
Tip 2 diyabet	7	36,8
Koroner arter hastalığı	2	10,5
Kalp yetmezliği	1	5,3

Tablo 2. *Hastaların başvuru semptomlarının dağılımı*

Semptomlar	Sayı (n)	Hasta yüzde (%)
Terleme	8	42,1
Baş ağrısı	8	42,1
Çarpıntı	7	36,8
Karın ağrısı	3	15,8
Flushing	3	15,8
Nefes darlığı	3	15,8
Öksürük	1	5,3
Ateş	1	5,3

Tablo 3. *Hastaların başvuru anındaki laboratuvar değerleri*

Parametreler	Değerler	Referans değer
Adrenokortikotrop hormon (pg/ml)	24,2 (6,5–164)	0–46
Kortizol (µg/dl)	12,6 (10,2–21,5)	6,7–22,6
1 mg deksametazon supresyon testi (µg/dl)	1 (0,6–3)	
Dihidroepiandrostenodion sülfat (µg/dl)	96,5 (15–321)	167,9–591,9
Plazma aldosteron/PRA oranı	6,3 (0,3–14,7)	
Tiroid Stimulan Hormon (ulU/ml)	1,2 (0,5–3,5)	0,3–5,3
Kalsiyum (mg/dl)	10,2 (8,9–10,5)	8,8–10,6
Sodyum (mEq/L)	140 (134–146)	136–146
Potasyum (mEq/L)	4,6 (4,1–5,2)	3,5–5,1
25 (OH) D (µg/L)	13 (4–26)	

PRA, plazma renin aktivitesi.

Tablo 4. *Hastalara ait 24 saatlik idrarda ölçülen hormon ve metabolit değerleri*

	Yüksek n (%)	Normal n (%)
Normetanefrin (µg/24 saat)	16 (%94,1)	1 (%5,9)
Vanil mandelik asit (mg/24 saat)	7 (%70)	3 (%30)
Metanefrin (µg/24 saat)	10 (%58,8)	7 (%41,2)
Dopamin (µg/24 saat)	8 (%50)	8 (%50)
Epinefrin (µg/24 saat)	2 (%20)	8 (%80)
Norepinefrin (µg/24 saat)	2 (%20)	8 (%80)

Tablo 5. *Hastaların radyolojik ve patolojik bulguları*

Özellik	Sayı (n)	Hasta yüzde (%)
Tümör yerleşimi		
Sağ	11	57,9
Sol	5	26,3
Bilateral	3	15,8
Radyolojik görüntüleme		
USG	2	10,5
BT	6	31,5
MRG	10	52,6
MIBG sintigrafisi	1	5,3
Radyolojik tümör boyutu		
<40 mm	7	36,8
40–60 mm	8	42,1
>60 mm	4	21,1
Patolojik tümör boyutu		
<40 mm	7	36,8
40–60 mm	8	42,1
>60 mm	4	21,1

USG, ultrasonografi; BT, bilgisayarlı tomografi; MRG, manyetik rezonans görüntüleme.

kanseri olan toplam sekiz hastaya genetik inceleme yapıldı. Yapılan genetik inceleme sonucunda bir hasta MEN 2A tanısı aldı.

Tartışma

Feokromositoma kromaffin hücrelerinden kaynaklanan, katekolamin salgılayan nadir görülen nöroendokrin tümörlerdendir. Her iki cinsiyette eşit sıklıkta görülür ve en çok 4. ve 5. dekadlarda tanı alırlar. Bizim çalışmamızda da ortalama görülme yaşı 44,1±11,3 saptanmış olup literatür ile benzer saptandı[6,12,13]. Çalışmamızda kadın hastalarda daha fazla oranda görülmesinin sebebinin çalışmanın az sayıda vaka içermesi olabilir.

Amerika'da yürütülen bir çalışmada feokromasitoma hastalarına en sık eşlik eden hastalık olarak hipertansiyon ikinci sıklıkla diyabet saptanmıştır[14]. Literatür değerlendirildiği zaman olgu sunumları şeklinde subakut tiroidit, Graves hastalığı ve papiller karsinomun feokromasitomaya eşlik ettiği gözlenmiştir[15–17]. Ayrıca Türkiye'de yapılan bir çalışmada feokromasitoma hastalarının %12,5'inde tiroid nodülü saptanmıştır[18]. Bizim çalışmamızda da en sık komorbid hastalık olarak hipertansiyon saptanırken ikinci sıkılıkla tiroid patolojileri, üçüncü sıklıkta diyabet saptanmıştır. Ayrıca bu çalışmanın sonucunda feokromasitoma hastalarında tiroid patolojilerinin diyabetten daha sık gözlendiğini saptanmış olup bu hastaların tiroid patolojileri yönünden değerlendirilmesi gerekliliğini ortaya koymuştur.

Feokromasitomalar salgıladıkları hormonlar ve peptidler aracılığı ile paroksismal yada persistan hipertansiyona neden olur. Literatür incelendiği zaman hastaların yaklaşık yarısında sustain hipertansiyon saptanırken %45'inde paroksismal hipertansiyon mevcuttur[19,20]. Hastaların %5–15 kadarında tansiyon normal saptanabilir[21–23]. Tansiyon yüksekliği ile başvuran hastaların yalnızca %0,1'i feokromasitoma tanısı almaktadır ve hastalık çok farklı klinik özellikler gösterebilmektedir. Nadir görülmesi ve farklı klinik özelliklere sahip olmasından dolayı tanı koymak zor olabilir. Bu çalışmada da literatür ile uyumlu olarak hastaların %52,6'sında hipertansiyon öyküsü mevcuttu ve %42,1'inde hipertansiyon ilk başvuru anında saptandı. Hastaların %15,8'inde başvuru esnasında tansiyon normal sınırlarda saptandı. Bu sonuç bize feokromasitoma hastalarında tansiyonun normal sınırlarda olabileceğini ve hipertansiyon yokluğunun hastalığı ekarte ettirmeyeceğini göstermektedir.

Feokromasitoma hastalarının en sık başvuru şikâyeti paroksismal ya da persistan tansiyon yüksekliğidir. Tansiyon yüksekliği ile başvuran kişilerde terleme, baş ağrısı ve çarpıntıdan oluşan semptom triadının bulunması feokromasitomanın en sık görülen klinik prezentasyonudur[5,24,25]. Hastaların kliniği bu triad dışında, hormon salgılanma özelliklerine, çeşitliliğine ve bireylerin katekolamin duyarlılığındaki farklılıklara bağlı olarak değişkenlik gösterebilir[12,23,26,27]. Literatür ile uyumlu olarak bizim çalışmamızda da hastaların en sık başvuru şikayeti tansiyon yüksekliği olarak saptandı ve tansiyon yüksekliğine klasik semptom triadının eşlik ettiği gözlendi. Yine de çalışmamız daha önceki çalışmalarda olduğu gibi feokromasitoma semptomlarının çok değişken olabileceğini ve hastaların karın ağrısı, nefes darlığı, öksürük gibi farklı semptomlarla da başvurabileceğini gösterdi.

Olgularımız arasında tiroid medüller kanser tanısı ile takipli iken tansiyon atakları nedenli tetkik edilen, her iki sürrenal bezde kitle saptanan ve feokromasitoma tanısı konması üzerine yapılan genetik incelemede ailesel sendromlardan MEN 2A kabul edilen bir olgumuz bulunmaktaydı. Literatür incelendiğinde MEN 2A sendromlarında %25 olguda önce feokromasitoma, %40,2 olguda ise önce medüller tiroid kanseri tanısı konulduğu, hastaların %34,7'sinde ise iki hastalığın birlikte tespit edildiği belirtilmektedir[28,29].

Literatürde elektrolit imbalansı ile başvuran feokromasitoma olguları olmasına rağmen karakteristik bir elektrolit bozukluğu bildirilmemiştir. Hiperkalsemi, feokromositomanın nadir görülen bir komplikasyonudur ve literatürde vaka sunumları olarak bahsedilmektedir[30,31]. Feokromasitoma hastalarında eş zamanlı hiperparatiroidizm (MEN) olması veya PTH-ilişkili protein üretimi hiperkalsemiye neden olabilir[32–34]. Bu çalışmada olguların elektrolit değerleri literatür ile uyumlu olarak normal sınırlarda saptandı ve karakteristik bir elektrolit bozukluğu gözlenmedi. Epidemiyolojik veriler yüksek 25 (OH) D3 seviyelerinin farklı kanser türlerinde azalmış prevalans ve mortalite ile ilişkili olduğunu göstermiştir[35,36]. Feokromasitoma hastalarında 25 (0H) D düzeyini değerlendirilen bir çalışma literatürde saptanmamıştır. Sadece birkaç vaka raporunda 25 (0H) D düzeyinin düşük bulunduğundan bahsedilmiştir[37,38]. D vitamini ile adrenal bozukluklar arasındaki ilişki az çalışılmış bir konudur ve bu konuda bilimsel literatür yetersizdir. Bu çalışmada hastaların hepsinde vitamin D düzeyi 30 μg/L altındaydı. Ülkemizin vitamin D eksikliğinin endemik görüldüğü ülkelerden birisi olması bu durumu açıklayan sebeplerden biri olabilir[39]. Bu konuda daha kesin bir sonuca varabilmek için daha fazla sayıda hasta içeren kontrollü çalışmalara ihtiyaç vardır.

Laboratuvar tanısında özellikle atak sırasında alınan kanda ve bu sırada toplanmaya başlanan 24 saatlik idrarda katekolamin ve metabolitlerinin düzeyinin artmış olarak bulunmasının %100'lere varan sensitivite oranlarına sahip olduğu bildirilmektedir[9,40,41]. Fraksiyone metanefrinlerin idrar veya plazmada ölçümü, katekolaminlere göre daha yüksek sensitiviteye sahiptir[40,42]. İdrar testleri daha yaygın olarak ve sıklıkla başlangıç testi olarak kullanılır[1]. Normotansif ve asemptomatik bir hastada idrar ve plazma katekolamin ve metabolitlerinin düzeylerinin normal olması, feokromositoma tanısını ekarte ettirmez, fakat hipertansif ve semptomatik bir hastada tanıdan büyük ölçüde uzaklaştırır[2]. Bu çalışmada da plazma normetanefrin düzeyi hastaların %94,1'inde yüksek saptandı ve literatür ile uyumluydu[2,40,42].

Feokromositoma varlığı biyokimyasal olarak kanıtlandıktan sonra, tümörün yerleşim yeri saptanmalıdır. Bu amaçla en sık BT ve MR kullanılır. Bazı durumlarda fonksiyonel görüntüleme modaliteleri uygulanabilir. BT ve MR ile görüntülemenin sensitivitesi yüksek (%95–100), fakat spesifitesi düşüktür (%50–70)[2]. BT ile 0,5–1 cm'den büyük adrenal kitleler veya 1–2 cm'den büyük adrenal dışı feokromositomalar, özellikle 2–5 mm kalınlıkta çekildiğinde saptanabilir. Kontrastsız BT görüntülemesinde dansite 10 Hounsfield (genellikle >25) üstündedir. MR görüntülemesinde feokromositoma T2-ağırlıklı görüntülerde karaciğere göre belirgin hiperintens görüntü verir ve extraadrenal feokromositomaların tanısında BT'ye göre daha değerlidir. Ayrıca MR ile görüntülemenin kontrast madde verilmemesi, hipertansif kriz olasılığının düşük olması ve radyasyon maruziyetinin daha az olması gibi avantajları vardır. BT veya MR ile tek taraflı adrenal kitle tespit edildiğinde kitlenin fonksiyonel olarak görüntülenmesine gerek yoktur. Laboratuar testleri feokromasitoma ile uyumlu olgularda abdominal görüntülemelerin negatif çıkması durumunda fonksiyonel görüntüleme yapılır[1,2,43,44]. Bu çalışmada feokromastioma hastaların %84,1'inde BT ve MR ile lokalize edilirken %10,5'inde USG ile lokalize edildi. Hastaların on sekizinde feokromasitoma abdominal görüntülemeler ile lokalize edilmiş olup bir hastada fonksiyonel görüntülemeye ihtiyaç duyulmuştur.

Yapılan çalışmalar incelendiğinde feokromasitomanın genellikle sağ bezde yerleştiği ve 4 cm'den büyük olduğu gözlenmiştir[24,45–47]. Yüzde 10 oranında bilateral olarak gözlendiği saptanmıştır[2,24,45]. Bu çalışmada da feokromasitomanın daha çok sağ adrenal bezde yerleştiği ve genellikle 4 cm'den büyük olduğu saptandı ve önceki çalışmalar ile uyumlu bulundu. Bilateral feokromasitoma önceki çalışmalara benzer şekilde saptandı.

Bu çalışmanın çeşitli kısıtlamaları mevcuttu. Öncelikle çalışma tasarımı retrospektifti ve dosyalar geçmişe doğru taranarak incelendi. Hastaya uygulanan cerrahi teknik (açık ya da laparoskopik) tüm hastalarda bilinmemektedir. Hastalar operasyon sonrasında değişik merkezlerde de takibe devam ettikleri için uzun dönem sonuçları tam olarak bilinmemektedir. Uzun dönem sonuçları iyi bilinmediği için uygulanan tedavinin ya da başlangıçtaki parametrelerin nüks üzerinde etkisi olup olmadığı incelenemedi.

Sonuç olarak feokromasitomalar nadir görülseler de tedaviye dirençli, ataklar şeklinde hipertansif krizlerle seyreden ve dördüncü-beşinci dekadda ortaya çıkan tüm olgularda akla getirilmelidir. Klinik belirgin olmasa bile aksi ispat edilene dek adrenal kitlelerin feokromasitoma olabileceği unutulmamalıdır. Bu nedenle tüm adrenal kitleler feokromasitoma açısından değerlendirilmelidir. Feokromasitoma için tarama testi olarak öncelikle 24 saatlik idrarda normetanefrin ve metanefrin düzeyi istenmeli ve normal

saptanan olgularda feokromasitoma şüphesi devam ediyorsa diğer katekolamin metabolitleri değerlendirilmelidir. Tarama testlerinde normetanefrin ve metanefrin düzeyleri değerlendirilmeden adrenalin ve noradrenalin düzeylerinin istenmesinin maliyeti artırmak dışında ek yararı yoktur. Feokromasitomanın uygun koşullarda yapılan klinik, laboratuvar ve görüntüleme yöntemleri ile tanısının konabileceği ve uygun şekilde yapılan cerrahi ile kür olabileceği unutulmamalıdır.

Çıkar Çatışması

Herhangi bir çıkar çatışması yoktur.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of the Level of Serum Irisin in Patients With Gestational Diabetes Mellitus

Gestasyonel Diabetes Mellitusta Serum İrisin Düzeyinin Araştırılması

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ABSTRACT

Aim: *In pregnancy, the most common metabolic disorder is Diabetes Mellitus (DM). Gestational diabetes mellitus (GDM) is glucose intolerance that first appears during pregnancy or is diagnosed. Especially in late pregnancy, the fetüs, rapidly growing glucose metabolism, directs glucose and amino acids to the fetus. The mother's energy needs are arranged in the provision (free fatty acids, ketones, and glycerol) from alternative sources. It is the irisin the main function is turning from white adipose tissue to brown adipose tissue, uncover energy as heat and induced by exercises, such as weight loss, reduction in insulin resistance, associated with obesity, glucose regulation and effects on lipid metabolism are known to have many physiological properties. This study, it is aimed to investigate the level of irisin, which is GDM involved in energy metabolism, a new hormone.*

Material and Method: *In Firat University Faculty of Medicine, Obstetrics and Gynecology Clinic, the 40 pregnant women diagnosed with GDM (Group 1) and 40 healthy pregnant women without any problems in pregnancy (Group 2) so that the total 80 patients were included in this study. These groups were divided into four subgroups, GDM in the second trimester, 20 patients (Group 1A), GDM in the third trimester, 20 patients (Group 1B), In the second trimester, 20 healthy patients (Group 2A), In the third trimester, 20 healthy patients (Group 2B).*

Results: *In this study compared with control groups, serum irisin levels were increased significantly, including the 2. trimester higher (263.70±127.69 ng/ml) in the GDM group. There was no correlation between serum irisin level and BMI.*

Conclusion: *In future studies, the necessity of questioned physical activity and exercise, the need for more extensive experimental and clinical studies, and if the pathophysiological mechanisms between the iris and GDM are illuminated, the clinical conclusion was reached irisin related options can be treated.*

Key words: *pregnancy; gestational diabetes mellitus; irisin; body mass index*

ÖZET

Amaç: *Gebelikte en sık karşılaşılan metabolizma bozukluğu Diabetes Mellitus (DM)'dur. Gestasyonel Diabetes Mellitus (GDM) gebelikte ilk kez ortaya çıkan veya gebelik sırasında tanı konulan glukoz tolerans bozukluğudur. Özellikle gebeliğin son dönemlerinde glukoz metabolizması, hızla büyümekte olan fetüse glukoz ve aminoasitleri yönlendirerek annenin enerji ihtiyacının alternatif kaynaklardan (serbest yağ asitleri, ketonlar ve gliserol) sağlanması şeklinde düzenlenir. Temel fonksiyonu beyaz yağ dokusunu, kahverengi yağ dokusuna çevirerek enerjinin ısı olarak ortaya çıkmasını sağlamak olan ve egzersizle uyarılan irisin; kilo kaybı, insülin direncinde azalma, şişmanlık ile ilişkili olması, glukozun düzenlenmesi ve lipid metabolizmasında ki etkileri gibi birçok fizyolojik özelliğinin olduğu bilinmektedir. Bu çalışmada; GDM'li hastalarda enerji metabolizmasında görev alan yeni bir hormon olan irisin düzeyinin incelenmesi amaçlanmıştır.*

Materyal ve Metot: *Çalışmaya Fırat Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniğinde GDM tanısıyla takip edilen 40 gebe (Grup 1) ve gebeliğinde herhangi bir problemi olmayan sağlıklı 40 gebe (Grup 2) olmak üzere toplam 80 hasta dahil edildi. Bu gruplar da kendi içerisinde GDM'li ikinci trimesterinde 20 hasta (Grup 1A), GDM'li üçüncü trimesterinde 20 hasta (Grup 1B) ve sağlıklı ikinci trimesterinde 20 hasta (Grup 2A), sağlıklı üçüncü trimesterinde 20 hasta (Grup 2B) olmak üzere 4 alt gruba ayrıldı.*

Bulgular: *Çalışmamızda kontrol gruplarıyla karşılaştırıldığında 2. trimesterda daha yüksek olmakla üzere (263,70±127,69 ng/ml) GDM gruplarında serum irisin düzeyleri anlamlı olarak artmış bulundu.*

Sonuç: *İleride yapılacak çalışmalarda fiziksel aktivite ve egzersizin sorgulanmasının gerekliliği, daha kapsamlı deneysel ve klinik çalışmalara ihtiyaç olduğu ve GDM ile irisin arasındaki fizyopatolojik mekanizmalar aydınlatılabildiği takdirde klinik olarak irisin ile ilgili tedavi seçeneklerinin olabileceği kanaatine varılmıştır.*

Anahtar kelimeler: *gebelik; gestasyonel diabetes mellitus; irisin; vücut kitle indeksi*

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Introduction

Gestational Diabetes Mellitus (GDM) is a glucose tolerance disorder that first appeared during pregnancy or was diagnosed during pregnancy[1]. It is the most common metabolic disorder during pregnancy. In the baby, congenital malformation and intrauterine death can cause consequences. GDM is a metabolic disorder that can cause increased morbidity and mortality due to different disorders such as hypoglycemia, diabetic ketoacidosis, retinopathy, neuropathy, and nephropathy in the mother[2].

As it is known, many metabolic and hormonal changes occur during pregnancy. The main purpose of these changes is to provide the fetus with sufficient energy. It is known as the first-trimester anabolic period and is when gluconeogenesis is increased. An increase characterizes maternal protein, glycogen, and fat stores. In this period, because insulin sensitivity increases, there is a tendency to hypoglycemia and ketosis. The second half of pregnancy is the catabolic period. Maternal metabolism is affected by placental hormones. With the effect of these hormones, carbohydrate use decreases, lipolysis increases, maternal adipose mass decreases, and insulin resistance dominate the table. While the mother uses glycerol, free fatty acids, and ketones as the main energy source, Glucose and amino acids are stored for the need of the fetus[3,4]. As the week of pregnancy progresses, insulin resistance increases. Human placental lactogen (HPL), progesterone, cortisol, growth hormone, and prolactin are the most important anti-insulin hormones that cause insulin resistance[2,5]. In response to developing insulin resistance, pancreatic beta cells develop hyperplasia, and insulin secretion increases[6–8]. However, it is unable to respond to secretion.

One of the hormones involved in energy metabolism is the 112 amino acid peptide irisin, discovered by Bostrom et al. in 2012[9]. The exercise-induced iris is synthesized from muscle tissue, and it converts white adipose tissue to brown adipose tissue, revealing energy in the form of heat[10]. Irisin causes a decrease in insulin resistance and affects glucose and lipid metabolism[11,12]. It has been demonstrated a protective role in nutritional obesity and diabetes in experimental animals[9].

This study aims to examine the level of irisin, a new hormone involved in energy metabolism in patients with GDM.

Materials and Methods

After obtaining the necessary ethics committee permission from the Firat University Faculty of Medicine Clinical Research Ethics Committee with the date-decision number 02.08.2013/02-02, Between the ages of 18–40 and At 24–28 weeks of pregnancy, who were followed up in the Firat University Faculty of Medicine Hospital between August 2013 and March 2014 total of 80 volunteer participants were included in our study, including 40 cases with diagnosed with GDM and 40 healthy pregnant women. Informed consent was obtained from all patients. Both groups were divided into two subgroups: pregnant women in their second and third trimesters.

- Group 1 (n=40): Group with Gestational Diabetes Mellitus
- Group 1A (n=20): Pregnant women in the second trimester
- Group 1B (n=20): Pregnant women in the third trimester
- Group 2 (n=40): Healthy pregnant (control) group
- Grup 2A (n=20): Pregnant women in the second trimester
- Grup 2B (n=20): pregnant women in the third trimester

Demographic data (height, age, weight), body mass index, gravida, parity, number of abortions, systolic arterial blood pressures measurements (SAP), diastolic arterial blood pressures measurements (DAP), gestational week (Gw), and obstetric ultrasonographic information were recorded. Whole blood, biochemistry, and urine analyzes were performed and recorded.

Statistical analysis

SPSS 12.0 (The Statistical Package for the Social Sciences, Chicago, USA) program was used for statistical analysis. The data obtained were recorded as mean ± SD. Variation analysis (ANOVA) was used to analyze parametric tests, and a post-Tukey HSD test was used when a significant difference was found in the comparison between the groups. Paired t test was used to compare repetitive measurements within the group. Values with $P<0.05$ were considered statistically significant.

Results

Groups are similar in demographic data of patients (p>0.05) (Table 1). When BMI, systolic, and diastolic arterial pressure values were analyzed; There was no statistically significant difference between groups (p>005). Similarly, when gestational weeks were examined, no difference was found between the groups (p>0.05). In terms of gravida and parity; There was a statistically significant increase in Group 1A compared to Group 2A and Group 1B compared to Group 2B. (P<0.05). There was no difference in abortion between the groups (p>0.05).

When serum irisin levels were examined; It was found higher in the 2. trimester group with GDM (Group 1A) than the 2. Trimester healthy group (Group 2A). Likewise, in the 3. The trimester grup with GDM (Group 1B) was significantly higher than the 3. trimester healthy group (Group 2B) (p<0.05). In the comparison within the group, the iris level was statistically higher in both groups in the 2nd trimester (p<0.05). When we look at the correlation between body mass index and iris; Weak negativity in the GDM group (r= -0.075, -0.19), whereas in the control group, weak positivity (r=0.33, 0.03) was found, but it was not statistically significant. Demographic, Clinical, and biochemical data are given in Table 1.

Discussion

The main purpose of metabolic changes in the mother during pregnancy is to provide the fetus with enough energy. It is known as the first-trimester anabolic period and is characterized by increased gluconeogenesis, maternal protein, glycogen, and fat stores. The energy stored in the first trimester is used to meet the needs of the growing fetus in later periods. Fasting blood glucose level is lower due to the peripheral use of glucose increases. The second half of pregnancy is the catabolic period and increased HPL secreted by syncytiotrophoblasts. HPL increases lipolysis in adipose tissue, and glucose and amino acids are stored for the fetus' s need. HPL, progesterone, cortisol, and prolactin are hormones responsible for insulin resistance and act by disrupting the glucose uptake of insulin-sensitive cells. However, it is known that there is no decrease in insulin receptors during pregnancy[10].

Pregnancies complicated by diabetes are risky pregnancies that require close monitoring both maternally and fetally. When adequate glycemic control cannot be achieved, it can cause congenital malformations and in-utero death in the baby. The mother is a metabolic disorder that can cause morbidity and mortality due to increased hypoglycemia, diabetic ketoacidosis, retinopathy, and nephropathy.

Table 1. *Demographic, clinical and biochemical data*

	Grup 1 (n=40)		Grup 2 (n=40)	
	Grup 1A (n=20)	Grup 1B (n=20)	Grup 2A (n=20)	Grup 2B (n=20)
Age (year)	29.75±3.87	35.45±5.94	26.40±5.78	29.55±6.41
Weight (kg)	72.75±12.31	74.55±11.98	68.00±7.00	73.38±11.4
Length (cm)	161.00±6.05	162.05±6.34	162.90±6.39	161.30±5.42
Irisin (ng/ml)	263.70±127.69 [a]	192.29±84.84 [b]	201.06±87.8	129.33±53.8
BMI	27.73±4.13	28.41±4.56	25.58±2.02	28.23±4.56
Gw	25.50±1.23	35.50±3.31	23.90±2.33	33.20±3.44
SAP (mmHg)	108.50±16.63	113.75±16.04	113.75±12.7	109.75±8.80
DAP (mmHg)	71.00±11.19	70.50±9.98	69.23±9.77	70.75±8.31
Gravida*	2 (1–6) [a]	4 (1–9) [b]	1 (1–4)	2 (1–5)
Parite*	2 (1–6) [a]	2 (0–9) [b]	0 (0–2)	1 (0–3)
Abortus *	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–3)

* Median (minimum-maximum), values are given as mean ± standard deviation. BMI, Body mass index; GW, Pregnancy week; SAP, Systolic blood pressure; DAP, Diastolic blood pressure; [a] Compared to Group 2A. [b] Compared to Group 2B (p<0.05).

It plays a role in peptides called adipokine and myokin in energy metabolism. One of the newly discovered myokines is irisine and plays a role in energy and thermogenesis[9]. By releasing the irisin from the muscle, it turns the white adipose tissue into brown adipose tissue and plays an important role in energy consumption and thermogenesis[13,14]. In addition, it was observed that the iris caused weight loss and an increase in oxygen consumption[9]. It also has positive effects on glucose metabolism[9]. In this study, we aim to investigate the level of irisin in patients with gestational diabetes mellitus.

In this study, serum irisin level in comparison between groups; was found higher in the 2nd-trimester group with GDM than the healthy 2nd-trimester group. In addition, the 3rd-trimester group with GDM was significantly higher than the 2nd-trimester healthy group. In the comparison within the group; In both groups, irisin levels in the 2nd trimester were found to be statistically higher.

Similar to our study, Ebert et al. found that average irisin levels were higher in patients with GDM in their study on 148 patients, including 74 GDM and 74 healthy pregnant women[14]. Likewise, Gümüş et al. found that serum irisin levels were higher in the GDM group than healthy group[13]. However, Kuzmicki et al. compared 130 GDM and 140 control groups in their study and found that serum irisin concentration was significantly increased in pregnant women but markedly lower in women with GDM[15]. Similar to this study, Guardiola-Diaz et al. and Hojlund et al. found a statistically significant low in patients with type 2 DM[16,17]. Serum irisin levels were found low in type 2 diabetes in a study by Choi et al.[18]. It has been concluded that the iris can play an important role in glucose intolerance and type 2 diabetes. Aydin et al. likewise found that serum irisin levels decreased significantly in patients with GDM and thought that this decrease was associated with insulin resistance[19].

These studies were in contrast with our findings. This contrast in our study may be due to some controversial limitations and different treatment protocols of patients with GDM. Also, due to the exercise levels of the patients being unknown, different results may be obtained because exercise is an essential factor in the secretion of the iris. Gümüş et al. evaluated irisin levels with the frequency of exercising in his study and found that irisin levels in the exercising group were statistically significantly higher than the non-exercising group[13]. Similarly, in animal studies, it was found that irisin levels increased with exercise stimulation[20]. As a result of these studies, it can be said that physical activity and exercise reveal the necessity of questioning thoroughly.

In our study, when the correlation between irisin level and body mass index and irisin was examined, a low negative correlation was observed in the GDM group, and a low positive correlation was observed in the control group. However, this correlation was not statistically significant. Stengel et al. As a result of the study involving individuals with anorexia nervosa and obese individuals; A positive correlation has been reported between BMI and irisin levels[21]. As a result of their study, they also found that iris levels had a positive correlation with BMI. they concluded that the main factor contributing to serum irisin levels in body fat mass[22]. Gümüş et al. Similarly, their studies have shown a positive relationship between irisin level and BMI values before pregnancy[13].

Conclusion

Our study; We found that serum irisin levels were significantly higher in GDM pregnant women compared to control groups, and there was no correlation between BMI and irisin. However, more comprehensive experimental and clinical studies are needed. We believe there may be treatment options related to irisin clinically if physiopathological mechanisms between GDM and irisin can be elucidated.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Bladder Distention due to Electrocautery Knife Use in Spine Surgery: The First Experimental Study

Omurga Cerrahisinde Elektrokoter Bıçağı kullanımına bağlı İdrar Kesesi Distansiyonu: İlk Deneysel Çalışma

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ABSTRACT

Aim: *In our study, we aimed to examine the mechanism of ACA/sacral parasympathetic network injury and its effects on the bladder, which have not been included in the literature before, due to the use of electrocautery knife in spinal surgery.*

Material and Method: *Twenty hybrid rabbits were used in our study. Five of the animals were evaluated as the control (control group). Surgery was performed on 6 of them using bipolar electrocautery knife (BEC group) and 9 using monopolar electrocautery knife (MEC group). Th11-L2 spinal laminectomy was performed on animals during surgery. Animals were sacrificed after bladder tomography was taken one week later. After sacrification, the bladder and Onuf nucleus/S4 spinal ganglia were taken for histopathological examination. Bladder volume values and S4 ganglion density values were compared statistically using the Man Whitney-U test.*

Results: *Bladder volume values were found to be 48±5 cm^3 in the control group. It was found to be 52±6 cm^3 in the BEC group and 75±9 cm^3 in the MEC group. S4 dorsal root ganglion densities were 8±3/mm^3 in the control group and 143±23/mm^3 in the BEC group, and It was found to be 643±75/mm^3 in the MEC group. The results were statistically significant.*

Conclusion: *As a result of the findings we obtained in our study, we recommend that the high-voltage MEC/BEC electrocautery blade should not be used in spine surgery unless it is necessary due to its dangerous effects on AKA, sacral parasympathetic network, and consequently, the urogenital system.*

Key words: *spinal surgery; electrocautery knife; bladder*

ÖZET

Amaç: *Çalışmamızda literatürde daha önce yer almayan, omurga cerrahisinde elektrokoter bıçağı kullanımına bağlı, AKA/sakral parasempatik ağ hasarı oluşma mekanizması ve mesane üzerindeki etkilerini incelemeyi amaçladık.*

Materyal ve Metot: *Çalışmamızda 20 hibrit tavşan kullanıldı. Hayvanlardan beşi kontrol (Kontrol grubu) olarak değerlendirildi. Altı tanesine bipolar elektrokoter kullanılarak (BEC grubu), dokuz tanesine monopolar elektrokoter kullanılarak (MEC grubu) cerrahi müdahale yapıldı. Cerrahi müdahalede hayvanlara Th11-L2 spinal laminektomi yapıldı. Bir hafta sonra hayvanların mesane tomografileri çekildikten sonra hayvanlar sakrifiye edildi. Sakrifikasyon sonrası hayvanların mesanesi ve Onuf nukleus/S4 spinal gangliyonları histopatolojik inceleme amaçlı alındı. Mesane hacim değerleri ve S4 gangliyon dansite değerleri Man Whitney-U testi kullanılarak istatistiksel olarak karşılaştırıldı.*

Bulgular: *Mesane hacim değerleri kontrol grubunda 48±5 cm^3 olarak saptandı; BEC grubunda 52±6 cm^3 ve MEC grubunda 75±9 cm^3 olarak bulundu. S4 dorsal root gangliyon dansiteleri kontrol grubunda 8±3/mm^3, BEC grubunda 143±23/mm^3; MEC grubunda 643±75/mm^3 olarak bulundu. Sonuçlar istatistiksel olarak anlamlı olarak saptandı.*

Sonuç: *Çalışmamızda elde ettiğimiz bulgular sonucunda yüksek voltajlı MEC/BEC elektrokoter bıçağını, AKA, sakral parasempatik ağ ve sonuç olarak ürogenital sistem üzerine olan tehlikeli etkileri nedeniyle zorunlu olmadıkça omurga cerrahisinde kullanılmamasını önermekteyiz.*

Anahtar kelimeler: *spinal cerrahi; elektrokoter bıçak; mesane*

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Introduction

The sacral parasympathetic network provides parasympathetic innervation of the urinary system. The sacral parasympathetic bladder motoneurons are located in the Onuf's nucleus in the sacral spinal cord, which Onufrowitz first described in 1899[1]. Lower spinal arterial circulation is provided Adamkiewicz artery (AKA) described in 1882 by Adamkiewicz[2]. As a result, AKA provides the circulation of the sacral parasympathetic network.

Vasospasm may develop after spinal subarachnoid hemorrhage (SAH) in AKA[3]. AKA vasospasm causes degeneration in the onuf's nucleus/pudendal ganglia due to circulatory failure, and therefore, urinary retention may occur[4]. There may also be intestinal involvement due to AKA vasospasm[5]. As can be understood from these studies, ACA, which provides arterial circulation to the onuf nucleus and dorsal root ganglia (DRG), is very important for abdominopelvic organ functions.

Electrical devices are used for tissue cutting or coagulation in surgeries, and they can be hazardous for live tissues. The mechanism of electrical injury can be explained by thermal damage, vascular impairment, and histological or electrophysiological changes in peripheral nerves or direct electromechanical trauma[6]. With the application of electrocautery, ACA can be affected as circulatory disorders and thrombus development in the radicular arteries[7]. Monopolar (MEC) or bipolar electrocautery knife (BEC) used in spine surgery are examples of commonly used electrical devices. Although MEC and BEC are used frequently, they can cause serious tissue damage like other electrical surgical instruments.

We aimed to show that high voltage BEC/MEC application affects ACA and consequently causes bladder pathology due to neural dysfunction in our study.

Materials and Methods

Twenty male hybrid rabbits (2 years old and weighing 3.5–0.4 Kg) were used in our study. Experiments were done according to the approval of the ethical committee of Ataturk University. Five of the animals were allocated for the control group. The remaining animals were anesthetized by general anesthesia (25 mg/kg ketamine hydrochloride, 15 mg/kg lidocaine hydrochloride, and 1 mg/kg acepromasine). After the required surgical cleaning of the operation site, Th11-L2 laminectomy was applied, and facets were denervated. MEC was used in 8 animals (MEC group) and BEC in 7 animals during the surgical intervention. MEC and BEC were performed with an electrocaugulator of 220 V-50Hz. Fascia and skin sutured with 3–0 cotton sutures. Animals have followed their cages for seven days postoperatively without antibiotic/analgesic treatment. All animals were taken multislice CT to estimate urinary bladder volumes, and then all animals were sacrificed. S4 spinal ganglia and bladders were removed for histopathological examination. The S4 ganglia specimens and neurovascular bundles of bladders were embedded in paraffin blocks, and sections were stained with hematoxylin &eosin, tunnel, and aldehyde fuchsine. To estimate urinary bladder volume and Physical dissector method were estimated described by Yolas C et al.[4]. For neurodegeneration criteria, peri-cytoplasmic halo formation, cytoplasmic condensation, nuclear shrinking, and cellular angulations were accepted. To estimate Adamkiewicz artery degeneration, endothelial swelling, shrinkage, desquamation, and thrombus formation were taken as deformation criteria described by Aydin MD et al.[7]. The bladder is considered an ellipsoid shape, and its volume is estimated as same as the sphere's volume formula by averaging the x, y, z radii using spherical transformation methods. Statistical analysis between S4 ganglia degenerated neuron density, and bladder volume values were compared with the nonparametric Mann Whitney Test in SPSS 11.0 for Windows.

Results

The bladder tomography image, the macroscopic bladder view, and how we calculate the bladder volume are clearly shown in Fig. 1. Bladder volume values were detected as 48±5 cm^3 in normal, 52±6 cm^3 in BEC, and 75±9 cm^3 in MEC groups. Degenerated neuron density of S4 dorsal root ganglion (DRG) was 8±3 in control, 143±23/mm^3 in BEC, 643±75/mm^3 in the MEC group. $P<0.005$ between control/BEC; $p<0.0005$ between BEC/MEC and $p<0.00001$ between control/MEC (Table 1). Our results were found to be statistically significant.

Histopathologically, we detected adhesions and fibrotic scar in the peridural space at the operation area. While endothelial and muscle cell degeneration was seen in AKA animals using electrocautery, mainly

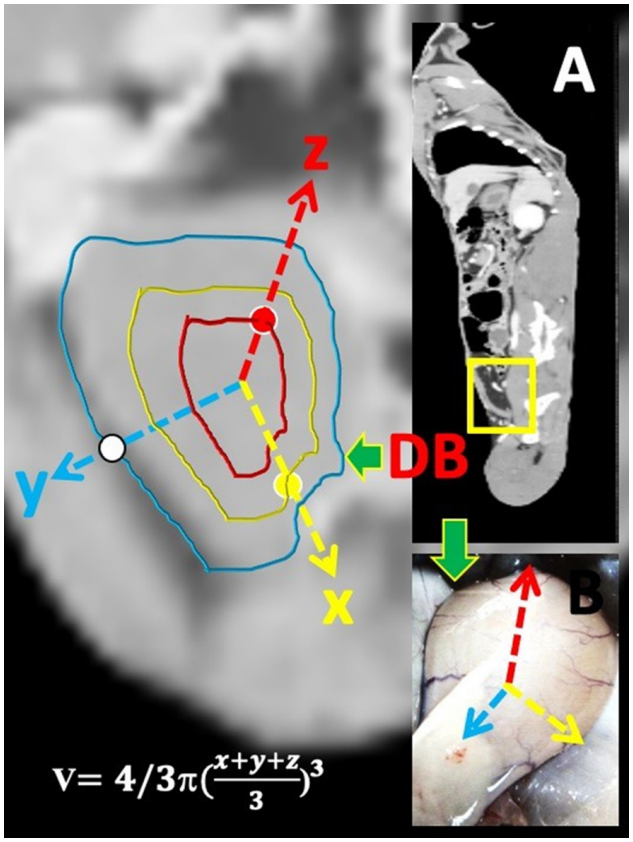

Figure 1. *The dilated bladder (DB) tomography image (A), the macroscopic bladder view (B), and the way we calculate the bladder volume (Base).*

Table 1. *Numerical bladder volume/cm³ and degenerated neuron density of DRG/mm³*

	Control Group	BEC Group	MEC Group
Bladder volume/cm³	48±5	52±6	75±9
Degenerated neuron density of DRG/mm³	8±3	143±23	643±75

MEC group: P<0.005 between control/BEC, p<0.0005 between BEC/MEC, and p<0.00001 between control/MEC.

in the MEC group, no effect was observed in the control group (Fig. 2). Especially in animals in the BEC group, apoptosis and degeneration were observed in neurons in DRG (Fig. 3). Likewise, while no involvement was found in the control group, thrombosis in the bladder arteries and degenerated/demyelinated pudendal nerve axons were evaluated more in the MEC group than in the BEC group histopathologically (Fig. 4).

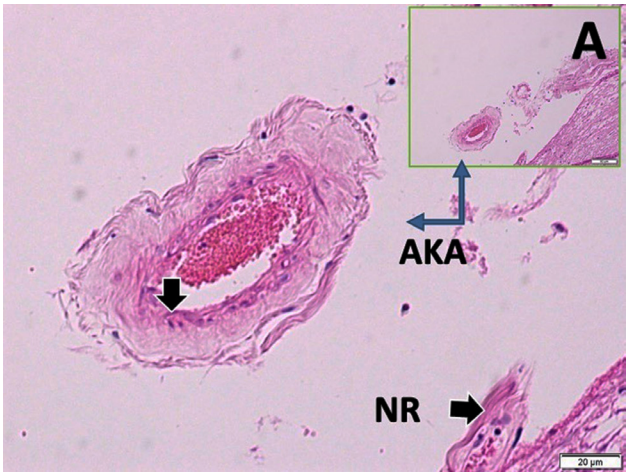

Figure 2. *Histopathological appearances of AKA (LM, H&E, x4/A) and magnified form with degenerated endothelial and muscle cells, nerve root (NR) (LM, H&E, x40/Base) are seen.*

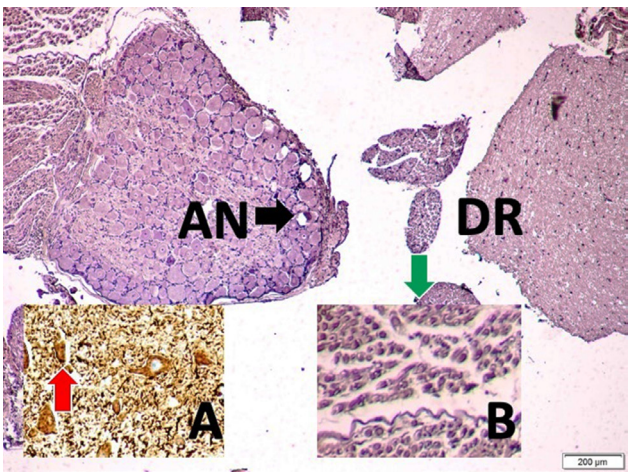

Figure 3. *Histopathological appearance of L4 dorsal root ganglion (DR), apoptotic neuron (AN) (LM, H&E, x10/Base); degenerated or loosened axons (LM, Tunel, x10/A) and apoptotic neurons of L4 roots are seen in a MEC applied animal (LM, Tunel, x10/B).*

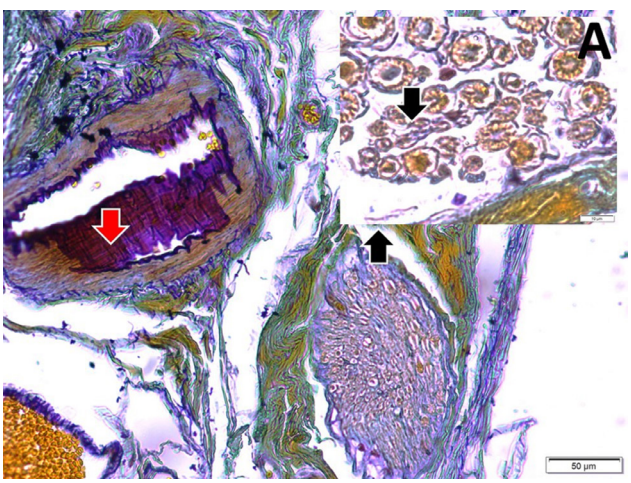

Figure 4. *Histopathological appearances of urinary bladder supplying thrombosed arteries (red arrow) (LM, VonGiezon, x20/Base) and degenerated/demyelinated pudendal nerve axons (black arrow) (LM, VonGiezon, x20/A) are seen.*

Discussion

Electrocautery knives are widely used in spine surgery as MEC or BEC form for soft tissue dissection and thermocoagulation; however, electrical currents have detrimental effects on neural[8] and vascular tissues[9].

In Bladder Innervation**,** the sacral parasympathetic bladder motoneurons are located in the Onuf's nucleus in the sacral spinal cord, and AKA provides the arterial circulation of these neurons. Distal extensions of the dorsal root ganglia travel with the pelvic and hypogastric nerves and through the pudendal nerves that enter the urethra[10] and the bladder to the bladder for filling and emptying. Afferent urinary bladder fibers are located in a suburothelial plexus, bladder neck, and the trigone six and function as stretch receptors stimulator to start micrution reflex[11]. Sacral parasympathetic stimulate detrusor smooth muscles for bladder contraction to start micturition[12]. It is seen that these functions will be affected with onuf nucleus damage due to the effect of ACA.

Although it was discovered nearly a century ago, we think the importance of the onuf nucleus is not sufficiently understood. Serious studies will be needed to realize the indispensable importance of the Adamkiewicz arterial network, which provides the basic blood support of the neurovascular network, especially the Onuf nucleus complex and the dorsal root ganglia of this region.

Unexplained urogenital complications can occur even after the safest spine surgery. We think that our study sheds light on urogenital complications whose cause cannot be understood after spine surgery. This situation has not been included in the literature before. It further increases the importance of our study results.

We recommend that BEC and MEC not be used during spinal surgery because of their harmful effects unless necessary. In cases where it is needed, it would be more appropriate to choose bec instead of mec, as it has a less harmful impact.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of the Covid-19 Pandemic on Traumatic and Non-traumatic Orthopedic Practice in a Tertiary Care Center: A Descriptive Cross-Sectional Study

Üçüncü Basamak Bir Hastanede Covid-19 Pandemisinin Travmatik ve Travmatik Olmayan Ortopedik Hastalıklara Etkisi: Tanımlayıcı Kesitsel Çalışma

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ABSTRACT

Aim: *Coronavirus (COVID-19) has emerged from Wuhan City, China, in 2019. Different precautions were taken in different territories and cities because of the diverse demographic structures of Turkey. In this study, the epidemiological prevalence of orthopedic traumatized and non-traumatized cases was assessed in a rural region of Turkey during the pandemic.*

Material and Method: *Between September 2019 and December 2020, 15452 patients were admitted to the clinic of orthopedics and traumatology with trauma, were evaluated in this retrospective cohort study. According to the dates of admission to the clinic, the patients were divided into pre-covid and covid groups. Age, gender, and fracture types of patients were recorded.*

Results: *741 (4.8%) patients were admitted to our clinic due to orthopedic trauma in the pre-covid period. In comparison, 816 (5.3%) patients were admitted to our clinic due to the same problems in the covid period. There were statistically significant differences between groups in terms of gender (p<0.001), age groups (p<0.001), and the presence of orthopedic trauma (p<0.001).*

Conclusion: *In rural areas, during the Covid-19 outbreak, the number of orthopedic trauma experienced increased compared to the previous period. Despite this, a decrease was observed in non-traumatic cases presenting to the outpatient clinic during the Covid-19 pandemic.*

Key words: *COVID-19; fracture; orthopedics; pandemic*

ÖZET

Amaç: *Coronavirüs (COVID-19), 2019 yılında Çin'in Wuhan şehrinde ortaya çıktı. Türkiye'nin farklı demografik yapıları nedeniyle farklı bölge ve şehirlerde farklı önlemler alındı. Bu çalışmada, pandemi sırasında Türkiye'nin kırsal bir bölgesinde ortopedik travma geçirmiş ve travma geçirmemiş vakaların epidemiyolojik prevalansı değerlendirildi.*

Materyal ve Metot: *Bu geriye dönük kohort çalışmasında Eylül 2019 ile Aralık 2020 tarihleri arasında ortopedi ve travmatoloji kliniğine başvuran 15452 hasta değerlendirildi. Kliniğe başvuru tarihlerine göre hastalar pre-covid ve covid gruplarına ayrıldı. Hastaların yaş, cinsiyet ve kırık tipleri kaydedildi.*

Bulgular: *Pre-covid döneminde 741 (%4,8) hasta ortopedik travma nedeniyle kliniğimize başvurmuştu. Buna karşılık 816 (%5,3) hasta covid döneminde aynı sorunlardan dolayı kliniğimize başvurmuştu. Gruplar arasında cinsiyet (p<0,001), yaş grupları (p<0,001) ve ortopedik travma varlığı (p<0,001) açısından istatistiksel olarak anlamlı fark tespit edildi.*

Sonuç: *Kırsal kesimde Covid-19 salgını sırasında yaşanan ortopedik travma sayısı bir önceki döneme göre artış göstermiştir. Buna rağmen covid-19 pandemisi sırasında polikliniğe başvuran travmatik olmayan vakalarda azalma gözlendi.*

Anahtar kelimeler: *Covid-19; kırık; ortopedi; pandemi*

Introduction

Coronavirus (COVID-19) emerged from Wuhan City, China, in 2019[1]. After spreading worldwide, WHO announced the disease as a pandemic in March 2020[2]. Public health precautions like social isolation, social distancing, and curfew were promoted because of inefficiency in treatment to prevent the spreading of the virus[3].

Our hospital is a tertiary care center located in Turkey's east and is the only hospital that accepts patients with Covid-19 and other diseases. Some precautions such

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as cancellation of elective surgeries and restrictions in outpatient clinics were taken to continue orthopedics and traumatology service.

This study investigates orthopedic traumatic and non-traumatic cases by comparing the lockdown period caused by the Covid-19 pandemic and the same period of the previous year to guide personal and source distribution to maintain health infrastructure.

Materials and Methods

Fifteen thousand and four hundred fifty-two patients admitted to orthopedics and traumatology clinics with trauma in September 2019 – December 2019 and September 2020 – December 2020 were evaluated in this retrospective cohort study. Ethical approval was obtained from the Ethics Committee of Ağri Training and Research Hospital (number: 17, date: 11.11.2020). Our hospital's electronic digital archive was used to evaluate traumatic and non-traumatic cases admitted to the emergency department or outpatient clinic. Patients who applied for administrative purposes and patients with missing files or inadequate information were excluded from this research. International Statistical Classification of Diseases and Related Health Problems (ICD) 10 codes were used to analyze the fracture types of patients. Fracture types of traumatic patients are divided into proximal, diaphysis, and distal 1/3 regions of long bones. Rare fracture types and fractures of flat bones were recorded as only names of fracture but not as proximal, diaphysis, and distal. Patients were categorized into four groups according to age as pediatric (<18 years old), young adult (18 years old and older age – 35 years old), middle-aged (36–64 years old), and elderly (>64 years old). The patients were divided into two groups as pre-covid and covid periods, according to the date of admission to the clinic. The pre-covid group included patients admitted between September 2019 – December 2019, and the covid group included patients admitted between September 2020 – December 2020. The gender of patients was recorded. All data were recorded and analyzed statistically.

Statistical Analysis

IBM SPSS Statistics 23.0 for statistical analysis (IBM Corp., Armonk, NY, USA) programs were used to evaluate the findings obtained in this study. Demographic data and others were reported as frequency and percentages. The arithmetic means ± standard deviation was calculated for the numerical variables. The normalities of parameter distributions were assessed using Shapiro Wilk tests. Mann-Whitney U test and Student's t-tests were used to compare parameters between the two groups. Wilcoxon Signed-Rank tests were used for intragroup comparisons of non-normally distributed parameters. Pearson's chi-square test, Fisher's Exact tests, Fisher Freeman Halton test, and Yates Correction for Continuity were used to compare qualitative data. Significance was evaluated at $p<0.05$.

Results

The number of patients was 10426 (67.50%) in the pre-covid period, and the number of patients was 5026 (32.50%) during the covid period. The mean age of the patients was 33.90±20.36 (range: 0–110). There were 8268 (53.50%) male patients, and 7184 (46.50%) were female. Thirteen thousand eight hundred ninety-five patients (89.9%) applied with non-traumatic diseases, while 1557 (10.1%) patients were admitted due to trauma. The age distribution of the patients was evaluated under four categories. The number of patients in the pediatric (range: 0–17) group was 3495 (22.60%); the number of patients in the young-adult (range: 17–44) group was 7213 (46.70%); the number of middle-aged (range: 40–64) patients was 3316 (21.50%); The number of patients in the elderly (range: 65–110) age group was 1428 (9.20%) (Table 1).

There were 741 (4.8%) patients who were admitted to our clinic due to orthopedic trauma in the pre-covid period (Fig. 1) and 816 (5.3%) patients in the covid period (Fig. 2). The mean age of the patients admitted to our clinic due to orthopedic trauma in the pre-covid period was 23.82±18.96 (range: 0–98). 506 (3.30%) of the patients who applied due to orthopedic trauma in the pre-covid period were male, and 235 (1.50%) were female. The average age of the patients admitted to our clinic due to orthopedic trauma during the covid period was 23.75±19.31 (range: 0–97). In the covid period, 561 (3.60%) of the 816 patients who applied to our clinic due to orthopedic trauma were male, and 255 (1.70%) were female (Table 2).

A significant difference was found between the groups in terms of gender ($p<0.001$). A statistically significant difference was found between the groups in terms of the age groups ($p<0.001$). A significant difference was determined between the patients' admission periods and the presence of orthopedic trauma ($p<0.001$) (Table 3).

Table 1. *Distribution of age, gender and admission reason characteristics of patients in pre-covid and covid period*

		Period		
		Pre-covid Count n (%)	Covid Count n (%)	p-value
Gender	Male	5323 (34.4%)	2945 (19.1%)	<0.001*
	Female	5103 (33.0%)	2081 (13.5%)	
Age groups	Children	2264 (14.7%)	1231 (8.0%)	<0.001*
	Young-adult	4714 (30.5%)	2499 (16.2%)	
	Middle-aged	2375 (15.4%)	941 (6.1%)	
	Elderly	1073 (6.9%)	355 (2.3%)	
Trauma	Non-trauma	9685 (62.7%)	4210 (27.2%)	<0.001*
	Trauma	741 (4.8%)	816 (5.3%)	

n, number.
* p<0.05.

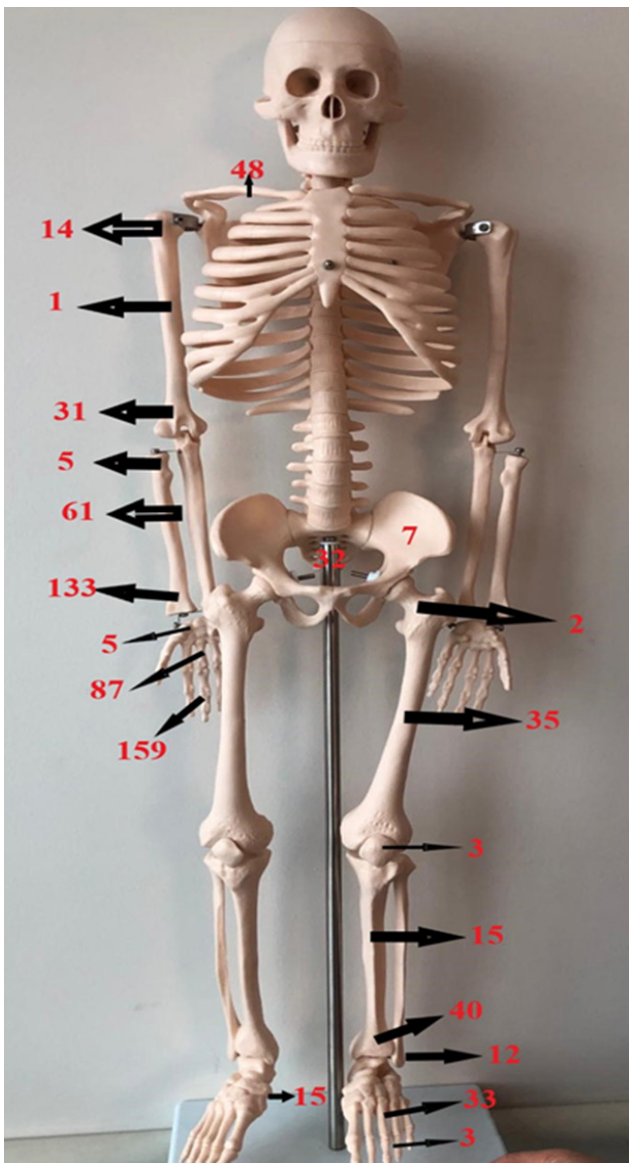

Figure 1. *Number of fractures during the Pre-covid period.*

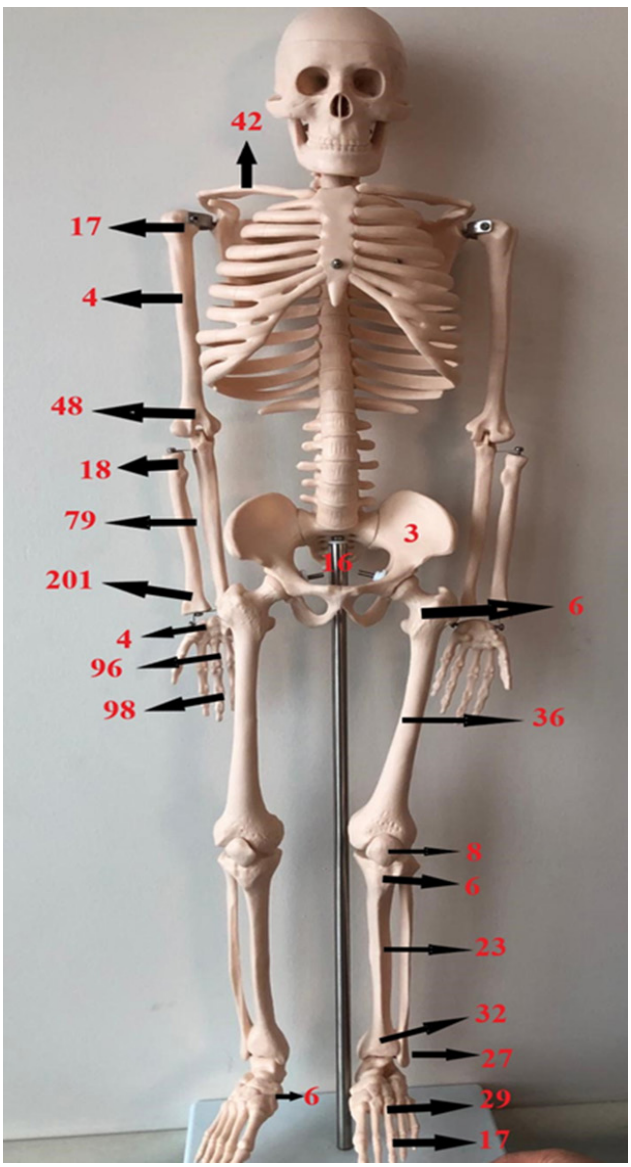

Figure 2. *Number of fractures during the Covid period.*

Table 2. *Comparison of gender and age groups between trauma and non-trauma cases*

		Non-trauma		Trauma		
		Pre-covid Count n (%)	Covid Count n (%)	Pre-covid Count n (%)	Covid Count n (%)	p-value
Gender	Male	4817 (31.2%)	2384 (15.4%)	506 (3.3%)	561 (3.6%)	<0.001*
	Female	4868 (31.5%)	1826 (11.8%)	235 (1.5%)	255 (1.7%)	
p-value		<0.001*		0.844		
Age groups	Children	1890 (12.2%)	823 (5.3%)	374 (2.4%)	408 (2.6%)	<0.001*
	Young-adult	4468 (28.9%)	2215 (14.3%)	246 (1.6%)	284 (1.8%)	
	Middle-aged	2291 (14.8%)	854 (5.5%)	84 (0.5%)	87 (0.6%)	
	Elderly	1036 (6.7%)	318 (2.1%)	37 (0.2%)	37 (0.2%)	
p-value		<0.001*		0.886		

n, number.
* p<0.05.

Table 3. *Distribution of the fracture types between groups*

	Period			
Fracture types	Pre-covid Count n (%)	Covid Count n (%)	Total	p-value
Coccyx fracture	32 (2.1%)	16 (1.0%)	48 (3.1%)	<0.001*
Pelvic ring fracture	7 (0.4%)	3 (0.2%)	10 (0.6%)	<0.001*
Clavicle fracture	48 (3.1%)	42 (2.7%)	90 (5.8%)	<0.001*
Proximal humeral fracture	14 (0.9%)	17 (1.1%)	31 (2.0%)	<0.001*
Humeral diaphysis fracture	1 (0.1%)	4 (0.3%)	5 (0.3%)	0.001
Distal humeral fracture	31 (2.0%)	48 (3.1%)	79 (5.1%)	<0.001*
Proximal radial fracture	5 (0.3%)	18 (1.2%)	23 (1.5%)	<0.001*
Forearm diaphysis fracture	61 (3.9%)	79 (5.1%)	140 (9.0%)	<0.001*
Distal radial fracture	133 (8.5%)	201 (12.9%)	334 (21.5%)	<0.001*
Scaphoid fracture	5 (0.3%)	4 (0.3%)	9 (0.6%)	<0.001*
Metacarpal fracture	87 (5.6%)	96 (6.2%)	183 (11.8%)	<0.001*
Phalangeal fractures of hand	159 (10.2%)	98 (6.3%)	257 (16.5%)	<0.001*
Proximal femoral fracture	2 (0.1%)	6 (0.4%)	8 (0.5%)	<0.001*
Femoral shaft fracture	35 (2.2%)	36 (2.3%)	71 (4.6%)	<0.001*
Tibia shaft fracture	15 (1.0%)	23 (1.5%)	38 (2.4%)	<0.001*
Distal tibia fracture	40 (2.6%)	32 (2.1%)	72 (4.6%)	<0.001*
Lateral malleolus fracture	12 (0.8%)	27 (1.7%)	39 (2.5%)	<0.001*
Calcaneal fracture	15 (1.0%)	6 (0.4%)	21 (1.3%)	<0.001*
Metatarsal fracture	33 (2.1%)	29 (1.9%)	62 (4.0%)	<0.001*
Phalangeal fractures of foot	3 (0.2%)	17 (1.1%)	20 (1.3%)	<0.001*
Patella fracture	3 (0.2%)	8 (0.5%)	11 (0.7%)	<0.001*
Proximal tibia fracture	0 (0.0%)	6 (0.4%)	6 (0.4%)	NULL
Total	741 (47.6%)	816 (52.4%)	1557 (100.0%)	0.384

n, number.
* p<0.05.
NULL, test could not be computed because the standard deviation is 0.

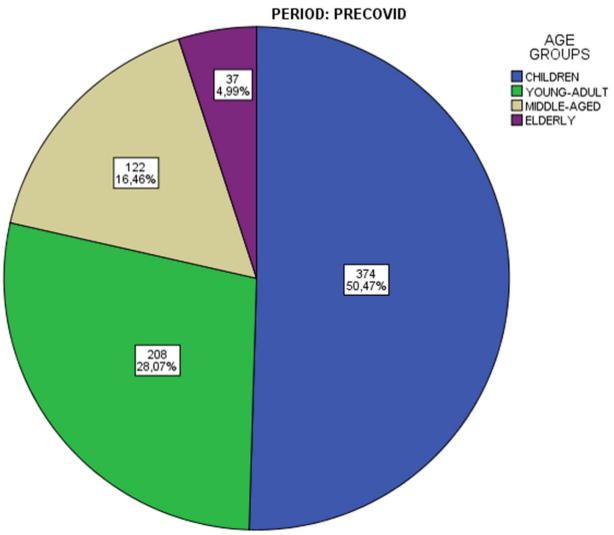

Figure 3. *Age groups during the Pre-covid period.*

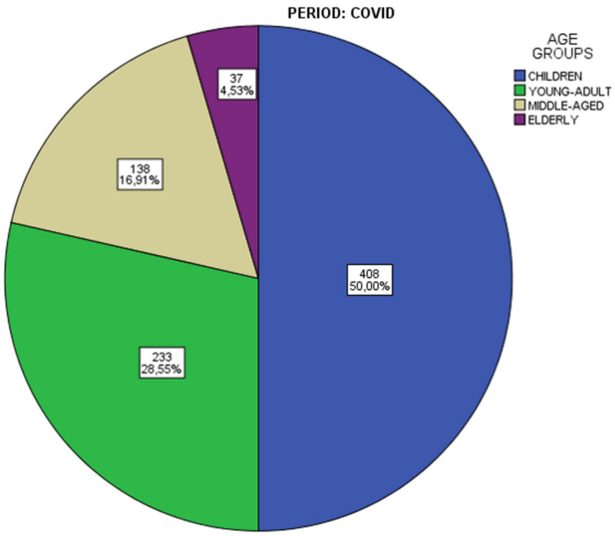

Figure 4. *Age groups during the Covid period.*

The orthopedic traumas of the patients were examined in 22 subgroups. The most noticeable fracture type was the distal radial fracture, with 334 (21.50%) patients in total. The second most common type of fracture was the phalangeal fractures of the hand, with 257 (16.50%) patients in total. Statistically significant differences were detected between patients' admission periods and orthopedic trauma causes except for the proximal tibia fractures ($p<0.001$). There was no statistically significant difference between the groups regarding the fracture types ($p=0.384$). There was no significant difference between the age groups and admission periods ($p=1.00$) (Fig. 3 and 4).

Discussion

The Covid-19 outbreak, caused by the Coronavirus-2 of Severe Acute Respiratory Syndrome (SARS-CoV-2), continues to impact societies and medical systems throughout the world[4]. Turkey is one of the countries that strive to decrease the devastating effects of the covid-19 pandemic. Some public health measures have been implemented, such as closing schools and workplaces. People are also afraid to go out. Therefore, we aimed to determine whether indoor injuries would increase and caused changes in the injury pattern in rural areas. Our medical center, which is in a rural location, is the only one in the territory that treats patients with the Covid-19 infection and orthopedic injuries. As a result of these circumstances, we conducted an epidemiological study of orthopedic trauma patients. We attempted to evaluate whether the number of traumatic and non-traumatic patients decreased or increased.

Leung et al.[5] stated that the number of admissions to hospital due to upper and lower extremity fractures decreased due to preventive measures and attempts to "stay home". They also noted that curfew could affect the risk of fracture due to reduced outdoor injuries. In a study from Iran, Kalantar et al.[6] indicated that the number of referred patients to the emergency room was significantly reduced. They also reported the number of orthopedic operations was also reduced to almost zero in March 2020. Our study found that the number of orthopedic trauma patients admitted to our hospital significantly increased, including upper and lower limb fractures excluding proximal tibia fractures in all populations. This finding was not compatible with the literature. The admission of non-traumatic orthopedic diseases to our outpatient clinic has also decreased significantly. We thought preventive efforts and people's concerns about these potentially contagious illnesses contributed to the decline in the number of patients. Nevertheless, we estimated that household and farmworker injuries increased, increasing traumatic incidents. Another reason was that people could not reach more prominent hospitals in the center because of the prohibition of intercity transportation and the increase in the burden of traumatic cases on our hospital.

In a study from Iran, they evaluated 628 patients with a mean age of 38.9±19.9 (range 1 to 96) years who were admitted to the orthopedic emergency departments of two centers, 482 (75.30%) of them were men, and 158 (24.70%) were women[7]. We evaluated 15452 patients in pre– covid and covid periods; 8268 (53.5%) were male, and 7184 (46.5%) were female. The mean age of all groups in our study was 33.90±20.36, and it was a younger population than this study.

We determined that distal radius fractures were the most common type of fracture in these two periods. The second most common fracture was phalangeal fractures of the hand. In a recent study, Wong et al.[8] detected a decrease in the number of patients with orthopedic trauma. Zhu et al.[9] reported that hip fractures after thoracolumbar fractures were the most common fracture types in the elderly population. In a multi-center study evaluating epidemic and control groups in China, authors determined that femur fractures followed by tibia and fibula fractures were the most common in the Covid-19 group. Femur fractures were also the most common in the control group, but the second most common fracture type was hand and foot fractures[10]. There was no statistically significant difference between fracture type and admission time of the two groups in our study. This outcome was a finding that we did not expect; indoor and outdoor injuries cause different types of fractures, and an increase in indoor injuries would change fracture type. Slullitel et al.[11] reported that elderly patients were less active and frailer. They also stated that this was associated with higher mortality and affected implant selection. We predicted that elderly patients were expected to be more prone to fractures, particularly the hip and distal radius. However, in our study, we could not find any significant difference between fracture types and age groups.

Because of "stay home" initiatives and special preventive measures for the pediatric group in our country, we detected a decrease in patients admitted to the emergency room or outpatient clinic for fracture treatment. Researchers evaluated the pediatric fractures' epidemiology in a study, and they determined a considerable reduction in lower limb fractures requiring operative treatment[12]. Raitio et al.[13] found that the number of pediatric fractures decreased 2.5 times during the covid-19 pandemic and stated that this was related to the decline in the usage of playgrounds and the discontinuance of sports activities. Our study was a retrospective study, and we could not categorize injury mechanisms, which was a limitation of our study. Before the Covid-19 outbreak, the amount of pediatric traumatic events treated ineffectively with alternative methods in this territory should not be ignored. Nevertheless, there was an increase in the number of hospitalized pediatric trauma patients. This finding was not consistent with the literature. We predicted that domestic injuries caused a rise in pediatric trauma.

There were some limitations to our study. This study was a retrospective study, and we were unable to categorize injury mechanisms. This study was also limited to a local area. Another limitation was that we evaluated data using ICD-10 codes, so some fractures cannot be detected. Besides, the injury mechanism of patients could not be assessed. The findings would be better if the researchers could examine the multicenter data.

In conclusion, we found an increase in the number of traumatic cases during the covid-19 period compared to the pre-covid period in the rural area of Turkey. However, we did not find any difference in fracture type rates in both groups. Furthermore, we detected a decrease in non-traumatic cases admitted to the outpatient clinic. Our study was the only study achieved in a rural area, evaluating both pre-covid and covid periods. This study suggests that doctors and hospital managers working in rural areas should be prepared for an increase in orthopedic injuries in similar disasters that may occur in the future.

Ethics Committee Approval

Ethical approval was obtained from the Ethics Committee of Ağri Training and Research Hospital (number: 17, date: 11.11.2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent

N/A.

Author Contributions

Concept – S. T. ; Design – S. T., H. Ö. ; Supervision – S. T., O. P. ; Materials – S. T., H. Ö., O. P. ; Data Collection and/or Processing – S. T., H. Ö., O. P. ; Analysis and/or Interpretation – S. T., O. P. ; Literature Search – S. T., H. Ö., O. P. ; Writing Manuscript – S. T. ; Critical Review – S. T., O. P.

Conflict of Interest

The authors have no conflicts of interest to declare.

Financial Disclosure

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Mid-term Comparison of Weight Loss and Nutritional Parameters After Laparoscopic Sleeve Gastrectomy and Roux-En-Y Gastric Bypass

Laparoskopik Sleeve Gastrektomi ve Roux-En-Y Gastrik Bypass Sonrası Kilo Verme ve Beslenme Parametrelerinin Ara Dönem Karşılaştırması

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ABSTRACT

Aim: *In treating obesity, the restrictive effects of laparoscopic sleeve gastrectomy (LSG) and malabsorptive effects of laparoscopic Roux-En-Y Gastric Bypass (LRYGB) are two distinct outcomes responsible for excess weight loss.*

Material and Method: *The data of 110 patients who underwent bariatric surgery for morbid obesity (Body Mass Index-BMI ≥40 kg/m^2) in our hospital between 2012 and 2017 and completed the 6-month follow-up period were retrospectively evaluated. According to the surgical procedure (LSG and LRYGB), the patients were divided into two groups, with 65 patients in the LSG group and 45 in the LRYGB group. The demographic characteristics of the patients in both groups, preoperative and postoperative weight, BMI, iron, and iron-binding capacity, ferritin, vitamin B12, folic acid, hemoglobin, 25-hydroxy vitamin D, and MCV levels were compared.*

Results: *There was no significant difference between the groups regarding preoperative and postoperative weight or BMI values and weight loss values at the 6th postoperative month (p>0.05). While all preoperative parameters were similar between the two operation groups, a decrease in serum iron and MCV values in the LRYGB group at the 6th postoperative month was statistically significant (p=0.014, p=0.031, respectively).*

Conclusion: *LSG and LRYGB operations can be accepted as effective surgical methods with similar mid-term results and success rates. Iron deficiency and related blood count changes can be seen more frequently in gastric bypass patients than those undergoing sleeve gastrectomy.*

Key words: *sleeve gastrectomy; gastric bypass; laparoscopy; bariatric surgery; weight loss; vitamin deficiency*

ÖZET

Amaç: *Obezite tedavisinde sleeve gastrektomide restriktif, Roux-En-Y Gastrik Bypass yönteminde ise malabsorbtif etkiler ön plandadır. Çalışmamızda LSG ve LRYGB grubundaki hastalarımızın preoperatif ve postoperatif dönemdeki kilo ve nutrisyonel parametrelerinin karşılaştırılması amaçlanmıştır.*

Materyal ve Metot: *2012–2017 yılları arasında Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesinde Genel cerrahi kliniğinde morbid obezite (Body Mass Index-BMI ≥40 kg/m^2) nedeniyle, bariatrik cerrahi uygulanan ve altı aylık takip dönemini tamamlayan toplam 110 hastanın verileri retrospektif olarak değerlendirildi. Hastalar uygulanan yönteme göre iki gruba ayrıldı (LSG ve LRYGB). LSG grubunda 65, LRYGB grubunda 45 hasta yer aldı. Gruplarda yer alan hastaların demografik özellikleri, preoperatif ve postoperatif dönemdeki kilo, BMI, demir ve demir bağlama kapasitesi, ferritin, vitamin B12, folik asit, hemoglobin, 25-hidroksi vitamin D ve MCV düzeyleri kaydedilip karşılaştırıldı.*

Bulgular: *Gruplar arasında hastaların ameliyat öncesi ve sonrası kilo ve BMI değerleri ve ameliyat sonrası 6. ayda kaybedilen kg değerleri açısından anlamlı fark bulunamadı (p>0,05). Ameliyat öncesi bütün parametreler her iki ameliyat grubu arasında benzerken, ameliyat sonrası 6. ayda LRYGB grubunda serum demir ve MCV değerlerindeki düşüş istatistiksel olarak anlamlı bulundu (sırasıyla, p=0,014, p=0,031).*

Sonuç: *Sonuç olarak, erken dönem sonuçları itibari ile LSG ve LRYGB ameliyatları benzer sonuçlara ve başarı oranlarına sahip etkili cerrahi metodlar olarak kabul edilebilir. Bariatrik cerrahi sonrası gastrik bypass uygulanan hastalarda erken dönemde demir eksikliği ve buna bağlı semptomlar sleeve gastrektomiye göre daha sık görülebilir.*

Anahtar kelimeler: *sleeve gastrektomi; gastrik bypass; laparoskopi; bariatrik cerrahi; kilo kaybı; vitamin eksikliği*

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Introduction

Obesity and its related comorbidities (such as hypertension, hyperlipidemia, and type 2 diabetes) are associated with high morbidity and mortality[1]. The nonsurgical treatment of morbid obesity, with diet, medical practices, and exercise, cannot achieve effective weight loss as surgery[2,3]. However, although effective weight loss and comorbidity resolution can be accomplished with several bariatric surgical interventions, no single method has been recognized as the gold standard[4].

LSG is a widely used method, recently gaining in popularity. LSG provides an effective weight loss and comorbidity solution in obesity management with its restrictive and hormonal effects[5,6]. Since the pylorus and duodenum are still secure after LSG, there is a lower vitamin and nutrient deficiency rate. On the other hand, LRYGB is the optimal malabsorptive operation technique, but it is also restrictive. Vitamin and nutrient deficiency is expected during the postoperative period[7–9] as a decrease in the amount of food taken leads to vitamin and nutrient deficiency due to malabsorptive effects[10–12].

Our study aimed to compare changes in weight and nutritional parameters of LSG and LRYGB operations in the preoperative and postoperative periods.

Material and Method

Between January 2012 and November 2017, the data of 110 patients who underwent bariatric surgery for morbid obesity (Body Mass Index-BMI ≥40 kg/m^2) and completed a 6-month follow-up period in Bursa Yüksek Ihtisas Training and Research Hospital General Surgery Clinic were retrospectively evaluated. According to the surgery method, the patients were divided into two groups, with 65 patients in the LSG group and 45 patients in the LRYGB group. Detailed information about LSG and LRYGB techniques was given to the patients preoperatively and written informed consent was obtained. The Declaration of Helsinki carried out our study, and ethics committee approval was obtained with several 2017–15/26 from the Uludag University Faculty of Medicine Ethics Committee before the study.

The study included patients between the ages of 18–65 with a pre-op BMI ≥40 and attended follow-up for six months was included in the study. Patients with a BMI of <40, those who underwent revision surgery, or those who did not have regular follow-up records were excluded from the study. Postoperatively, patients in both groups were enrolled in a dietician's nutritional program and prescribed multivitamin and nutrient support.

The demographic characteristics, comorbidity, preoperative and postoperative weight, body mass index (BMI), iron and iron-binding capacity, ferritin, vitamin B12, folic acid, 25-hydroxyvitamin D level, hemoglobin, and MCV (Mean Corpuscular Volume) levels were recorded and compared.

Statistical Analysis

The frequency and percentages from the descriptive criteria, the average from the location criteria, and the standard deviation from the common criteria were taken in research data analysis. Student-t-test (significance test of the difference between two means) was used to evaluate continuous data. The level of significance was taken as $p<0.05$.

Results

One hundred ten patients were included in our study. Laparoscopic surgery was performed on all patients without conversion to open surgery. No incidence of mortality was recorded in our patients in the postoperative period, and there was no case of significant early-period morbidity.

The age, gender, presence of comorbidity, preoperative and postoperative weight, and BMI data of the patients in the two groups were evaluated (Table 1). The LSG group was composed of 78.5% female and 21.5% male patients, with 86.7% female and 13.3% male patients in the LRYGB group. No statistical difference was observed between the groups regarding gender distribution ($p=0.266$). The mean age of the patients in the LSG group was 38.83±10.83, while the mean age was 37.48±10.94 years in the LRYGB group. Again, there was no statistically significant difference between the groups regarding age distribution ($p=0.526$).

The rate of comorbidity was 41.5% in the LSG group and 51.1% in the group that underwent LRYGB, but this was not statistically significant ($p=0.322$). There was also no statistically significant difference between the groups regarding preoperative and postoperative 6th-month weight or BMI values.

Iron, iron-binding capacity, ferritin, folate, B12, 25OH vitamin D, Hgb, and MCV levels in both groups were evaluated in the preoperative and postoperative 6th month (Table 2). While there was no

Table 1. *Age, preoperative and postoperative weight, BMI and weight loss values of the patients*

		LSG (n=65)	LRYGB (n=45)	P value
Age		38.83±10.83	37.48±10.94	0.526
Weight (kg)	Preoperative	123.50±15.68	122.46±14.83	0.727
	6th mounth	85.07±10.67	85.22±8.54	0.697
BMI (kg/m^2)	Preoperative	45.46±4.67	45.70±5.10	0.797
	6th mounth	31.31±3.53	32.05±3.04	0.254
Weight loss (kg)	6th mounth	38.43±8.84	36.71±10.58	0.357

LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic roux-en-y gastric bypass; BMI, body mass index, Student t test.

Table 2. *Preoperative and postoperative iron, iron binding capacity, ferritin, folate, vitamin B12, 25OH vitamin D, Hgb, MCV values*

		LSG (n=65)	LRYGB (n=45)	P value
Iron (µg/dl)	Preoperative	67.24±28.76	59.66±24.47	0.152
	6th mounth	74.09±33.53	59.38±25.00	**0.014**
Iron binding capacity (µg/dl)	Preoperative	296.64±82.00	315.97±83.39	0.230
	6th mounth	260.63±76.76	277.51±86.69	0.285
Ferritin (ng/ml)	Preoperative	61.34±54.89	59.73±77.12	0.898
	6th mounth	56.69±48.48	46.37±59.21	0.421
Folate (ng/ml)	Preoperative	8.73±4.71	8.58±4.31	0.866
	6th mounth	7.44±4.08	6.97±3.38	0.527
Vitamin B12 (pg/ml)	Preoperative	348.04±132.29	331.77±87.57	0.472
	6th mounth	281.64±83.38	323.73±137.62	0.071
25 OH vitamin D (ng/ml)	Preoperative	25.40±14.90	20.99±9.80	0.085
	6th mounth	26.63±15.96	21.78±11.09	0.081
Hemoglobin (g/dl)	Preoperative	13.62±1.62	13.29±1.37	0.270
	6th mounth	13.43±1.40	13.10±1.33	0.225
MCV	Preoperative	84.25±6.54	82.49±7.56	0.197
	6th mounth	84.82±6.46	81.92±7.34	**0.031**

LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic roux-en-y gastric bypass; MCV, mean corpuscular volume, Student t test.

statistically significant difference between the groups in the preoperative period, statistically significant decreases in serum iron and MCV values were observed in the LRYGB group at the postoperative 6th month (p=0.014 p=0.031, respectively).

Discussion

Obesity is a multifactorial disease impacted by socioeconomic and socio-cultural influences and biological factors[13,14]. The most effective and sustainable results in obesity treatment are provided by bariatric surgical interventions[15].

While bariatric surgical interventions are most frequently performed in women, gender does not appear to be a determinant for the method of bariatric surgery[16,17]. This is corroborated by our study, where most of our patients were female, and there was no statistically significant difference in gender between the LSG and LRYGB groups (p=0.266; p=0.526).

In our study, mean weight loss at the end of the sixth postoperative month was recorded as 38.43 kg in patients undergoing LSG and 36.71 kg in patients who received LRYGB. Accordingly, there was no statistically significant difference between the two groups regarding weight loss (p=0.357). In other studies comparing the results of LSG with LRYGB, weight-loss rates were also found to be similar. It has been emphasized that the efficacy of LSG surgery is no less than LRYGB and that it can be an ideal surgical method[16–18].

At the end of the sixth month, there was no statistically significant change in BMI between the groups: the average BMI decreased to 31.31 kg/m^2 in the LSG

group and 32.05 kg/m^2 in the LRYGB group. This is in line with other studies that have found no significant difference in BMI change between LSG and LRYGB methods in the first six-month period[18–21]. In our study, similar rates for both weight loss and change in BMI were noted for both surgical methods at the end of the first six months.

Vitamin and nutrient deficiency is a common consequence of bariatric surgery due to the restriction of stomach volume or the malabsorptive nature of the procedure[22]. In patients who do not receive regular multivitamin support, there may be decreases in vitamin B12 of 2–18% and Fe of 1–18%, and related to this, symptoms such as fatigue, chills, and anemia may develop[23]. A study by Gehrer et al. conducted on 138 patients showed a significant decrease after LRYGB surgery, especially in terms of vitamin B12, during a one-year follow-up[24]. Although in our patients, no significant difference was found in levels of vitamin B12 between the LSG and LRGB groups during the first six months following surgery, there was a decrease in ferritin and iron levels in patients in both surgery groups at six months. However, the decrease in iron and ferritin levels was only statistically significant in the LRYGB group (p=0.014). Multivitamin support is routinely given post-op; however, because of limited food intake during this period, a further possible nutrient deficiency could likely be prevented by prescribing iron preparations, particularly to patients undergoing gastric bypass surgery.

In sleeve gastrectomy surgery, a reduction in food intake is achieved by decreasing the stomach capacity[5,6]; in this case, no problems with food absorption are expected in the postoperative period. On the other hand, as malabsorption is an important feature of LRYGB surgery, vitamin and mineral deficiency is more likely to ensue after this procedure[25,26]. Additionally, removing the fundus of the stomach during sleeve gastrectomy causes a decrease in levels of ghrelin, a hormone associated with increased hunger and normally secreted from this area, causing patients to feel fewer food cravings[27,28].

After LRYGB surgery, deficiencies in vitamins and minerals such as calcium, 25 (OH) D3, iron, and vitamin B12 may occur due to malabsorption[25,26]. 25 (OH) D3 deficiency may be seen in 14–89.7% of patients after bariatric surgery[29]. In our study, there was no decrease in the average 25 (OH) D3 level in the postoperative period and no difference in mean 25 (OH) D3 levels between the two groups in the preoperative or postoperative periods. The reason for this was thought to be vitamin D replacement, which was initiated in our patients in the early post-op period (1st month postoperatively).

Limitations

The relatively low number of patients in the study groups and a follow-up period of only six months, without long-term results, are limitations of our study.

Following bariatric surgery in morbidly obese patients, vitamin and nutrient deficiency may develop in the follow-up period due to restriction in food intake or malabsorption. In primarily malabsorptive interventions such as the LRYGB method, a decrease in iron and related MCV values may be more pronounced. Therefore, it is thought that an adjustment in replacement therapy during follow-up should be considered according to the surgical method used.

Competing Interests

The authors declare that they have no competing interests.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Factors Affecting Nurses' Patient Safety Culture and Job Satisfaction: A Comparative Study

Hemşirelerin Hasta Güvenliği Kültürünü ve İş Doyumunu Etkileyen Faktörler: Karşılaştırmalı Bir Çalışma

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ABSTRACT

Aim: *This study was conducted to comparatively analyze factors affecting nurses' patient safety culture and job satisfaction.*

Material and Method: *This was a descriptive and cross-sectional study. The study sample comprised 260 nurses of two state hospitals and one university hospital in TRA2 in northeastern Turkey. Data were collected between August 2017 and March 2018. Data were collected using a Demographic Information Form, the Patient Safety Culture Scale and Job Satisfaction Scale in Nurses. ANOVA (F) and t test and the Mann–Whitney U and Kruskal-Wallis H tests were used for data analysis. Total scale score and subscale mean scores were also calculated. A correlation analysis was performed between nurses' patient safety culture and job satisfaction.*

Results: *The total Patient Safety Culture Scale and Job Satisfaction Scale mean scores were calculated respectively as 2.78±0.47 and 3.34±0.68. There was a statistically significant difference in Patient Safety Culture Scale and Job Satisfaction Scale scores between groups in terms of the independent variables "choosing the nursing profession of their own free will," "departmental position" and "skills-job match" ($p<0.05$). Also, a moderate and positive correlation was detected between nurses' job satisfaction and patient safety culture ($p=0.000$, $r=0.598$).*

Conclusion: *Thirty-one independent variables affecting nurses' patient safety and job satisfaction were identified. It was concluded that nurses who have a high patient safety culture have high job satisfaction.*

Key words: *job satisfaction; nursing; patient safety; quality of care*

ÖZET

Amaç: *Bu araştırma, hemşirelerde hasta güvenliği kültürünü ve iş doyumunu etkileyen faktörlerin karşılaştırmalı analizini yapmak amacıyla gerçekleştirilmiştir.*

Materyal ve Metot: *Araştırma tanımlayıcı-kesitsel olarak yapılmıştır. Araştırmanın örneklemini Türkiye'nin Kuzeydoğusunda TRA2'de yer alan iki devlet hastanesinde ve bir üniversite hastanesinde çalışan 260 hemşire oluşturmuştur. Çalışmanın verileri, Ağustos 2017 ile Mart 2018 tarihleri arasında toplanmıştır. Araştırma verileri "Tanıtıcı Özellikler Formu", "Hasta Güvenliği Kültürü Ölçeği" ve "Hemşirelerde İş Doyumu Ölçeği" kullanılarak elde edilmiştir. Veri analizinde parametrik testlerden Anova (F) ve t-Testi, non-parametrik testlerden Mann Whitney U ve Kruskal Wallis H testleri kullanılmıştır. Ayrıca ölçek toplam puan ve ölçek alt boyut puan ortalamaları hesaplanmıştır. Bunların yanı sıra "Hasta Güvenliği Kültürü" ile "Hemşirelerde İş Doyumu" arasındaki ilişkiye korelasyon analizi ile bakılmıştır.*

Bulgular: *Toplam puan ortalaması Hasta Güvenliği Kültürü Ölçeğinde 2,78±0,47, Hemşirelerde İş Doyumu Ölçeğinde ise 3,34±0,68 olarak hesaplanmıştır. Araştırmada ele alınan bazı bağımsız değişkenlerden "hemşirelik mesleğini seçme durumuna", "çalıştığı bölümdeki pozisyonuna" ve "işini yeteneklerine uygun bulma durumuna" göre Hasta Güvenliği Kültürü Ölçeği ve Hemşirelerde İş Doyumu Ölçeği her ikisinde de gruplar arasındaki fark istatistiksel olarak anlamlı bulunmuştur ($p<0,05$). Ayrıca hasta güvenliği kültürü ile iş doyumu arasında pozitif yönlü bir ilişki saptanmıştır ($p=0,000$, $r=0,598$).*

Sonuç: *Hemşirelerde hem hasta güvenliği kültürünü hem de iş doyumunu 31 bağımsız değişkenin etkilediği saptanmıştır. Yüksek hasta güvenliği kültürüne sahip olan hemşirelerin iş doyumlarının da yüksek olduğu sonucuna ulaşılmıştır.*

Anahtar kelimeler: *bakım kalitesi; hasta güvenliği; hemşirelik; iş doyumu*

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Introduction

Despite recent technological advances and an increase in the number of treatment and care facilities and of scientific studies, patient safety remains a major problem in the healthcare system[1]. The report titled "To Err is Human: Building a Safer Health System" released by the U. S. Institute of Medicine (IOM) in 1999 defines patient safety as "the prevention of harm to patients"[2]. According to the World Health Organization (WHO), one in ten patients in Europe is exposed to an avoidable injury or an adverse event in hospitals[1]. Annually, 421 million people receive inpatient care and approximately 42.7 million adverse events occur. Recent research shows that patient harm due to hospital care is the fourteenth cause of mortality and morbidity in the world[3]. Baker et al.[4] reported that 7.5% of adverse events occur in hospitals in Canada and that 37% of them is preventable. Not only does this cause a variety of problems for patients and their families and for healthcare professionals, it is also a serious economic burden on the health system[1]. Patient safety, therefore, remains to be an issue that should be addressed by both organizations and the community[5]. According to the document that was most recently revised in 2012 by the International Council of Nurses, patient safety is the key element in the provision of high-quality healthcare and nursing care[6]. Such issues as cost-effectiveness and quality care, early discharge and the care burden for patients with acute and chronic diseases are becoming more and more important in all healthcare systems worldwide. The increasing changes and expectations in healthcare delivery affect quality of care, nurses' job satisfaction and patients' perceptions of care[7]. Some of the environmental/organizational factors affecting job satisfaction in the existing literature are job quality, salary, staff safety, developmental and promotional opportunities, working conditions, management style, reward systems and relationships in the work environment[8–10]. Higher job satisfaction in nurses results in higher morale, higher institutional and occupational commitment, safe and higher quality of care and motivates nurses to continue to remain in the nursing profession[11]. Nurses' job satisfaction is an essential factor for nursing care institutes, which affects not only nursing quality but also patient satisfaction[12].

Aim

This study aimed to determine the factors affecting nurses' patient safety culture and job satisfaction and the correlation between the two.

The study sought answers to the following questions:

What are the independent variables that affect nurses' patient safety culture?

What are the independent variables that affect nurses' job satisfaction?

Is there a correlation between nurses' patient safety culture and job satisfaction?

Methods

Study Design

This was a descriptive and cross-sectional study.

Study Setting and Sample

The study population comprised 425 nurses from two state hospitals and one university hospital in TRA2 (Ağrı, Kars, Ardahan, Iğdır) in northeastern Turkey. This study applied no specific sampling method. Nurses who volunteered to participate in the study were included in the sample. Of the nurses, 317 were contacted and informed about the purpose and procedure of the study prior to participation. Of these, 44 nurses did not agree to participate, and 13 nurses failed to complete the data collection form. Therefore, the final study sample consisted of 260 (61.2%) nurses.

$$n = \frac{Nt^2pq}{d^2(N-1)+t^2pq} \quad \frac{425x(1,96)^2x0.5x0.5}{(0,05)^2x424+(1,96)^2x0.5x0.5} = 202$$

Data Collection Tools

Data were collected using three forms: 1) Demographic Information Form (DIF); 2) Patient Safety Culture Scale (PSCS); and 3) Job Satisfaction Scale in Nurses (JSSN).

Demographic Information Form (DIF)

The original form of the DIF consisted of 26 open-ended questions eliciting information on institution, age, gender, marital status, educational degree, unit of service, skills-job match, institutional quality works and receiving training on quality.

Patient Safety Culture Scale (PSCS)

The PSCS was developed and its validity and reliability was established by Türkmen et al.[13]. It is a four-point Likert-type scale consisting of 51 items. It has five subscales: 1) management and leadership;

2) employee behavior; 3) unexpected events and error reporting; 4) employee training; and 5) care environment. The mean scores of the total scale and its subscales are calculated for assessment. A mean score of ≤2 indicates negative patient safety culture while a mean score of ≥2 indicates positive patient safety culture. The reliability coefficient (Cronbach's alpha) of the PSCS was found to be 0.97[13].

Job Satisfaction Scale in Nurses (JSSN)

The JSSN was developed by Muya et al in Japan in 2014. It was adapted to the Turkish language, and its validity and reliability were established by Yilmaz and Yildirim[14]. It is a five-point Likert-type scale consisting of 27 items and four subscales: 1) positive emotions toward work; 2) appropriate support from superiors; 3) perceived significance in the workplace; and 4) pleasant working environment. The mean scores of the 27 items and the subscales are calculated for assessment. The closer the score is to five, the higher the job satisfaction. The Cronbach's alpha coefficient of the scale was determined to be 0.94[14].

Data Collection

The data were collected between August 1, 2017 and March 9, 2018. Data collection sessions were scheduled at the participants' convenience. Head nurses were informed prior to data collection. Participants were asked to complete the data collection form in the presence of the researcher. In the event that we could not contact a participant in order to collect the data, we were able to learn the work days and hours of these nurses off the shift list and scheduled appointments for data collection at their convenience. Day and time appointments were taken from the nurses who were not available at the time, and the data were collected.

Data Analysis

The gathered data were analyzed using the IBM Statistical Package for Social Sciences (SPSS) for Windows Version 20.0. DIF frequencies were calculated. The PSCS and JSSN total score and subscale scores were calculated for each participant. The Kolmogorov-Smirnov (*KS*) test was used to determine whether the data met the assumptions for parametric tests. ANOVA (*F*) and *t* test (*t*) were used for normally distributed data whereas the Kruskal-Wallis *H* (*KW*) and Mann-Whitney *U* (*Z*) tests were used for non-normally distributed data. Bivariate Spearman's correlation was used to determine the correlation between nurses' patient safety culture and job satisfaction. For the significance level of statistical tests, $p<0.05$ value is accepted.

Ethical Considerations

The study was approved by the Ethics Committee of the Faculty of Medicine of *** University (No: 80576354-050-99/89, Date: April 27, 2017). Written permission was obtained from the hospital management as well. All articles of Helsinki Declaration Principles were complied with in the research.

Nurses who voluntarily participated were informed about the purpose and procedure of the study, and they declared verbal consent to participate. In addition, written permission was obtained from the authors of the PSCS and the JSSN in order to use them as data collection tools in this study.

Results

Table 1 shows the participants' mean PSCS and JSSN total score and subscale scores, respectively. In this study, the internal consistency coefficients (Cronbach's alpha) of the PSCS and JSSN were 0.95 and 0.91, respectively. There was a moderate and positive correlation between the PSCS and JSSN scores ($p=0.000$, $r=0.598$).

Table 1. *Participants' mean PSCS and JSSN total score and subscale*

Scores	
	X† ± SD‡ (min–max)
PSCS total score	2.78±0.47 (1.12–4)
Subscales	
Management and leadership	2.77±0.54 (1–4)
Employee behavior	2.82±0.53 (1–4)
Unexpected events and error reporting	2.75±0.57 (1–4)
Employee training	2.82±0.60 (1–4)
Care environment	2.75±0.57 (1–4)
	X† ± SD‡ (min–max)
JSSN total score	3.34±0.68 (1.30–5)
Subscales	
Positive emotions toward work	3.46±0.73 (1.5–5)
Appropriate support from superiors	3.13±1.22 (1–5)
Perceived significance in the workplace	3.80±0.70 (1.5–5)
Pleasant working environment	2.67±0.97 (1–5)

† SD; standard deviation; ‡ X; mean; PSCS; patient safety culture scale; JSSN; job satisfaction scale in nurses.

Table 2 shows the participants' demographic and job-related characteristics, respectively. When the PSCS and JSSN scores for the subscales "spending enough time with family" and "personality type (Type A or Type B)" were compared, it was found that the difference between the groups was statistically significant (p<0.05). When the PSCS and JSSN scores for the subscales "choosing to be a nurse," "departmental position," "skills-job match," "participation in decision-making in the workplace," "loving being a nurse," "considering quitting" and "re-choosing nursing" were compared, it was found that the difference between the groups was statistically significant (p<0.05).

Table 3 shows the participants' satisfaction with some working conditions based on their PSCS and JSSN scores. When the participants' PSCS and JSSN scores for the subscales "working hours and shifts," "division of tasks," "workload," "work pace," "number of nurses," "number of physicians," "number of patients," "interpersonal relationships in the workplace," "the institution they work for," "the unit in which they work," "training programs provided for patient safety" and "income" were compared, it was found that the difference between the groups was statistically significant (p<0.05).

The participants' responses to questions on patient safety and quality. When the PSCS and JSSN scores for the subscales "presence of a patient safety committee in the institution," "having received training on patient safety before," "receiving training on patient safety in the institution," "wishing to serve on the patient safety committee," "finding the patient safety committee necessary," "reading the announcements on patient and staff safety," "receiving training on teamwork," "participating in staff orientation," "knowing about total quality management studies" and "receiving training on quality" were compared, it was found that the difference between the groups was statistically significant (p<0.05).

Discussion

Research shows that patient safety and job satisfaction were found to affect each other[15–17]. However, no studies have been conducted so far on the issue in Turkey. Also, this is the most comprehensive study dealing with a large number of independent variables on national and international PSCS and JSSN issues.

The participants' total PSCS mean score was 2.78 (SD=0.47), suggesting the presence of positive patient safety culture. According to Türkmen et al.[13], a PSCS score above two indicates the presence of positive patient safety culture. Research shows that mean PSCS scores range from one to four, and therefore, some studies report higher PSCS scores[18–20], while others report lower scores[21,22] than those of the participants in this study.

In a study conducted at two private hospitals in Istanbul, Turkey, which apply the Quality Standards in Health of the Turkish Ministry of Health[18], reported a mean PSCS score of 3.00 (SD=0.53), which is higher than that of the participants in this study. The hospitals in TRA2 in northeastern Turkey, where this study was conducted, lack some quality standards. Furthermore, have high labor turnover due to their location and geographical characteristics, which might explain the difference between the results of this study and those of Karaca and Arslan's study. On the other hand, Rizalar et al.[22] reported a mean PSCS score of 2.64 (SD=0.43), which is lower than that of the participants. In this study, more than 70% of the participants have received training on patient safety culture before, whereas it was about 50% in[22] study, which might account for the difference.

Moreover, in this study, the lowest PSCS subscale scores were found in "unexpected events and error reporting" and "care environment" (2.75; SD=0.57) while the highest were found in "employee behavior" (2.82; SD=0.53) and "employee training" (2.82; SD=0.60). Karaca and Arslan[18], Ertürk et al.[19], Rizalar et al.[22] and Yolcu et al.[21] reported similar results. The nurses' PSCS subscale scores for "unexpected events and error reporting" was the lowest in the studies of Karaca and Arslan[18] and Ertürk et al.[19], while their PSCS subscale scores for "unexpected events and error reporting" and "care environment" were the lowest in Rizalar et al.[22]. Karaca and Arslan[18] and Ertürk et al.[19] reported the highest scores in the PSCS subscale "employee training" while Rizalar et al.[22] reported the highest score in the PSCS subscale "employee behavior", which is similar to this study's results. In Yolcu et al.[21], the nurses' PSCS subscale scores for "care and technology" and "employee behavior" were the lowest and the highest, respectively. Gündoğdu and Bahçecik[23] found that approximately 70% of nurses did not report any errors in their units in the last year. This indicates that managers of health institutions should encourage their staff

Table 2. *Distribution of participants' PSCS and JSSN scores depending on their demographic and job-related characteristics*

		PSCS		JSSN	
Characteristics	n (%)	Median (S. E. *)	p**	Median/Mean (S.E.*)	p**
Gender					
Woman	231 (88.8)	2.80 (0.031)	0.880	3.33 (0.045)	0.525
Man	29 (11.2)	2.80 (0.092)	Z=-0.151	3.42 (0.131)	t=-0.637
Marital status					
Married	135 (51.9)	2.82 (0.040)	0.348	3.40 (0.056)	0.174
Single	125 (48.1)	2.78 (0.043)	Z=-0.938	3.28 (0.064)	t=1.363
Degree					
Vocational school of health	50 (19.2)	2.75 (0.064)	0.777	3.24 (0.084)	0.343
Associate	72 (27.7)	2.80 (0.047)	KW=1.098	3.40 (0.079)	F=1.115
Bachelor's	123 (47.3)	2.80 (0.046)		3.32 (0.066)	
Master's	15 (5.8)	2.84 (0.142)		3.57 (0.152)	
Spending enough time with family					
Yes	73 (28.1)	2.92 (0.056)	**0.002**	3.68 (0.069)	**0.000**
No	187 (71.9)	2.76 (0.034)	Z=-3.058	3.21 (0.049)	t=5.280
Self-reported personality type					
Type A (ambitious, impatient, etc.)	149 (57.3)	2.76 (0.039)	**0.035**	3.27 (0.059)	**0.045**
Type B (relaxed, patient, etc.)	111 (42.7)	2.84 (0.043)	Z=-2.114	3.44 (0.059)	t=-2.014
Choosing to be a nurse					
Willingly	170 (65.4)	2.82 (0.033)	**0.008**	3.46 (0.051)	**0.000**
Unwillingly	90 (34.6)	2.67 (0.055)	Z=-2.637	3.12 (0.071)	t=3.904
Departmental position					
Nurse	212 (81.5)	2.78 (0.032)	**0.011**	3.29 (0.047)	**0.014**
Head nurse	38 (14.6)	2.85 (0.074)	KW=9.003	3.55 (0.113)	KW=8.538
Supervisor Nurse/Assistant nursing service manager/Others	10 (3.9)	3.21 (0.112)		3.67 (0.179)	
Staff position					
Permanent	174 (66.9)	2.78 (0.036)	0.295	3.33 (0.053)	0.737
Contracted	86 (33.1)	2.82 (0.050)	Z=-1.047	3.36 (0.071)	t=-0.336
Unit of service					
Clinic/Service	147 (56.5)	2.80 (0.040)	0.349	3.33 (0.060)	0.415
Intensive care/Emergency/Operating room	71 (27.3)	2.76 (0.046)	KW=4.447	3.36 (0.061)	F=0.987
Management/Admin.	5 (1.9)	3.14 (0.107)		3.45 (0.224)	
Polyclinic	10 (3.9)	2.76 (0.210)		2.97 (0.190)	
Others	27 (10.4)	2.78 (0.109)		3.45 (0.161)	
Skills-job match					
Always	121 (46.5)	2.90 (0.041)	**0.000**	3.52 (0.060)	**0.000**
Sometimes	47 (18.1)	2.69 (0.065)	KW=26.762	3.11 (0.101)	F=6.185
Never	4 (1.5)	2.47 (0.172)		2.51 (0.411)	
Often	77 (29.7)	2.80 (0.051)		3.29 (0.073)	
Rarely	11 (4.2)	2.43 (0.141)		2.99 (0.149)	
Participation in decision-making in the workplace					
Always	141 (54.2)	2.86 (0.039)	**0.006**	3.43 (0.055)	**0.003**
Sometimes	96 (36.9)	2.78 (0.046)	KW=10.345	3.32 (0.067)	F=6.124
Never	23 (8.9)	2.55 (0.115)		2.90 (0.165)	
Working on weekends					
Yes	198 (76.2)	2.80 (0.033)	0.946	3.31 (0.048)	0.229
No	62 (23.8)	2.81 (0.065)	Z=-0.068	3.43 (0.088)	t=-1.205
Shifts					
Yes	187 (71.9)	2.80 (0.035)	0.544	3.29 (0.051)	0.079
No	73 (28.1)	2.82 (0.055)	Z=-0.607	3.46 (0.076)	t=-1.762
Loving the profession					
Yes	187 (71.9)	2.88 (0.033)	**0.000**	3.50 (0.046)	**0.000**
No	73 (28.1)	2.59 (0.055)	Z=-4.904	2.93 (0.074)	t=6.461
Considering quitting					
Yes	84 (32.3)	2.71 (0.052)	**0.016**	3.14 (0.077)	**0.001**
No	176 (67.7)	2.83 (0.035)	Z=-2.412	3.44 (0.049)	t=-3.309
Re-choosing to be a nurse					
Yes	77 (29.6)	2.90 (0.054)	**0.002**	3.66 (0.068)	**0.000**
No	183 (70.4)	2.76 (0.034)	Z=-3.052	3.21 (0.050)	t=5.114
Finding the profession stressful					
Yes	237 (91.2)	2.80 (0.031)	0.660	3.35 (0.044)	0.314
No	23 (8.8)	2.92 (0.105)	Z=-0.440	3.20 (0.156)	t=1.010
Mean age		28.64±7.36 (min: 19, max: 58)			

*S.E.; Standard error; **p<0.05; PSCS; patient safety culture scale; JSSN; job satisfaction scale in nurses.

Table 3. *Distribution of participants' PSCS and JSSN scores depending on their satisfaction with some working conditions*

		PSCS		JSSN	
Satisfied with	n (%)	Median (S. E. *)	p**	Median/Mean (S.E.*)	p**
Working hours and shifts					
Yes	125 (48.1)	2.88 (0.041)	**0.002**	3.63 (0.057)	**0.000**
No	135 (51.9)	2.75 (0.041)	Z=-3.029	3.19 (0.054)	Z=-6.165
Division of tasks					
Yes	134 (51.5)	2.92 (0.038)	**0.000**	3.63 (0.050)	**0.000**
No	126 (48.5)	2.71 (0.041)	Z=-4.949	3.03 (0.058)	t=7.760
Workload					
Yes	70 (26.9)	2.97 (0.059)	**0.000**	3.70 (0.070)	**0.000**
No	190 (73.1)	2.75 (0.032)	Z=-4.609	3.21 (0.048)	t=5.469
Work pace					
Yes	102 (39.2)	2.94 (0.046)	**0.000**	3.62 (0.059)	**0.000**
No	158 (60.8)	2.73 (0.036)	Z=-4.029	3.16 (0.054)	t=5.715
Number of nurses					
Yes	49 (18.8)	2.96 (0.071)	**0.002**	3.93 (0.086)	**0.000**
No	211 (81.2)	2.76 (0.031)	Z=-3.030	3.30 (0.045)	Z=-5.079
Number of physicians					
Yes	143 (55.0)	2.90 (0.040)	**0.000**	3.47 (0.056)	**0.001**
No	117 (45.0)	2.75 (0.041)	Z=-3.750	3.19 (0.062)	t=3.354
Number of patients					
Yes	108 (41.5)	2.96 (0.049)	**0.000**	3.61 (0.062)	**0.000**
No	152 (58.5)	2.74 (0.034)	Z=-4.344	3.15 (0.053)	t=5.639
Interpersonal relationships in the workplace					
Yes	187 (71.9)	2.84 (0.036)	**0.003**	3.46 (0.047)	**0.000**
No	73 (28.1)	2.71 (0.044)	Z=-2.948	3.03 (0.081)	t=4.705
Working for the institution					
Yes	137 (52.7)	2.96 (0.039)	**0.000**	3.64 (0.048)	**0.000**
No	123 (47.3)	2.67 (0.039)	Z=-6.394	3.00 (0.059)	t=8.464
Working in unit/service/department					
Yes	197 (75.8)	2.86 (0.035)	**0.000**	3.48 (0.045)	**0.000**
No	63 (24.2)	2.69 (0.046)	Z=-3.997	2.89 (0.084)	t=6.417
Training on patient safety					
Yes	152 (58.5)	2.94 (0.034)	**0.000**	3.54 (0.049)	**0.000**
No	108 (41.5)	2.54 (0.043)	Z=-7.034	3.06 (0.066)	t=6.040
Income					
Yes	80 (30.8)	2.94 (0.059)	**0.000**	3.66 (0.074)	**0.000**
No	180 (69.2)	2.75 (0.032)	**Z=-3.902**	3.20 (0.048)	**t=5.200**

*S.E.; Standard error; **p<0.05; PSCS; patient safety culture scale; JSSN; job satisfaction scale in nurses.

to report errors and unexpected events. Furthermore, nurses are thought not to have enough knowledge of safety precautions related to care environments.

Yilmaz and Yildirim[14] state that the closer the JSSN score is to five, the higher the job satisfaction. The participants' mean JSSN score was 3.34 (*SD*=0.68), indicating an above-average job satisfaction. Research shows that mean JSSN scores range from one to five, and therefore, some studies reported higher JSSN scores[14], while others reported lower scores[24,25] than those of the participants in this study. Yilmaz and Yildirim[14] reported a mean JSSN score of 4.00 (*SD*=0.56), which is higher than that of this study's participants. This might be due to the higher number

of high school graduate nurses in Yilmaz and Yildirim's study[14]. Yang et al.[24] reported a mean job satisfaction score of 2.51 (*SD*=0.98), which is lower than that of the participants of this study.

In this study, the lowest JSSN subscale score was found in "pleasant working environment" (2.67; *SD*=0.97) and the highest in "perceived significance in the workplace" (3.80; *SD*=0.70). The results reported by Yilmaz and Yildirim[14] are similar to this study's results. The subscale "pleasant working environment" consists of items about taking into consideration individual circumstances, balancing work and private life, having an appropriate number of personnel, receiving a sufficient salary and requests for days off. The low "pleasant working environment" subscale score, therefore, suggests that participants' expectations regarding these matters are not met. Since 2016, when the JSNN was adapted to the Turkish language and its validity and reliability were established, there have been no further studies using the scale.

There is a positive correlation between the PSCS and JSSN total scores[26]. Each independent variable that affects the PSCS also affects the JSSN, suggesting that there is a correlation between the two. There are no national studies, to the researchers' knowledge, that comparatively analyzes nurses' patient safety culture and job satisfaction; however, there are international studies that do[15,16,27–30]. They report that the higher the nurses' job satisfaction, the better the patient outcomes and the higher the patient safety. They, therefore, recommend that attempts and interventions to improve patient safety culture also take into account levels of nurses' job satisfaction.

Participants who is choses to be a nurse of their own free will, had higher departmental positions, always or often found their job appropriate to their skills and participate in decision-making in the workplace had higher PSCS and JSSN scores. Participants who were satisfied with working hours and shifts, division of tasks, workload and work pace, the number of nurses, the number of physicians and the number of patients, interpersonal relationships in the workplace, the institution they work for, the unit in which they work, and training programs provided for patient safety and income had higher PSCS and JSSN scores. Participants who love being a nurse, do not consider quitting, serve on the patient safety committee, have received training on patient safety in the institution they work for or before, consider the presence of a patient safety committee necessary, have participated in staff orientation and received training on teamwork and quality, spend enough time with their families, state that they would choose to be a nurse if they were given the chance, read the announcements on patient and staff safety, know about total quality management studies, had a high-quality education and have a Type B personality had higher PSCS and JSSN scores.

When the PSCS and JSSN scores for the independent variables stated above were compared, it was found that the difference between the groups was statistically significant ($p<0.05$). National or international studies have investigated the effects of a limited number of variables on nurses' patient safety culture and job satisfaction. No national or international studies have ever examined all of the independent variables that caused the significant differences observed in this study; therefore, the results are discussed in a limited context.

Wami et al.[31] reported that patient safety culture is correlated with weekly working hours, number of staff, teamwork, good communication, unexpected events and error reporting and participating in patient safety training, which is similar to this study's results. Ball et al.[15] reported that longer working hours showed a decline in patient safety. Alqattan et al.[32] reported that nurses who took training or courses regarding patient safety had significantly higher patient safety culture than those who did not. Dinçer[33] found that receiving training on quality increases patient safety culture.

Tilev and Beydağ[11] reported that the higher the number of working hours, the lower the job satisfaction, while Çalişkan[34] found that those who chose to be a nurse of their own free will have higher overall job satisfaction. Tambağ et al.[35] found that nurses who are satisfied with their department have higher job satisfaction than those who are not. Lorber and Savic[12] reported that head nurses who are involved in decision-making in the workplace and satisfied with working hours have higher job satisfaction than the ones who are not satisfied with working hours. Nurses who love their profession work more effectively and efficiently, resulting in higher job satisfaction and patient safety culture.

Limitations

The results can only be generalizable to the nurses of the hospitals where this study was conducted.

Conclusion

There is a moderate positive relationship between nurses' patient safety culture and job satisfaction. It was concluded that nurses who have a high patient safety culture have high job satisfaction.

Patient safety culture in institutions should be systematically evaluated and interventions should be undertaken to improve it. Training programs should be organized to raise awareness of patient safety. Hospital managers should find ways to eliminate factors that reduce nurses' job satisfaction and to increase their motivation. Working environments and weekly working hours and shifts should be arranged to improve nurses' job satisfaction. Interventions should be initiated to encourage nurses to report unexpected errors and adverse events.

Conflict of Interest

There are no conflicts of interest to disclose.

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Author Contributions

Study design: KO, AKA

Data collection: KO, AKA

Data analysis: KO, AKA

Manuscript writing: KO, AKA

Critical Review, and/or Revision: AKA

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Postoperative Bladder Functions of Patients Who Underwent Cesarean Hysterectomy Due to Placenta Accreta Spectrum

Plasenta Akreta Spektrumuna Bağlı Olarak Sezaryen Histerektomi Uygulanan Hastaların Postoperatif Mesane Fonksiyonlarının Değerlendirilmesi

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ABSTRACT

Aim: *Placenta accreta spectrum (PAS), which includes placenta accreta, increta, and percreta, defines an abnormal placental invasion. PAS is associated with increased mortality and morbidity and injury of adjacent organs such as the bladder, ureter, and bowel. The bladder is the most common injured organ in the literatüre. Our study aimed to evaluate the bladder functions after postpartum hysterectomy, which was performed for PAS.*

Material and Method: *This single-centered prospective study was performed between January 2016 and January 2018. A total of 81 patients who were planned for an elective cesarean section and underwent peripartum hysterectomy due to PAS were included. Due to the unavailable data, 22 patients were excluded. The patients were divided into two groups: patients with bladder injury (n=20) and those without bladder injury (n=25). Furthermore, the bladder injury group was subdivided into two subgroups as bladder injury ≥2 cm (n=8) and bladder injury <2 cm (n=12).*

Results: *There was no statistically significant difference between the two groups' sociodemographic characteristics. No significant difference was found between the two groups about laboratory parameters. There was no significant difference between the two groups according to the first sense to void, normal desire to void, bladder emptying time, maximum urethral pressure, bladder pressure, maximum urethral closure pressure, and residual volume (p>0.05) while strong desire to void (439.2±70.05 vs. 391±67.34, p=0.024) and maximum bladder capacity (400.8±65.76 vs. 351±57.39, p=0.011) were significantly lower in bladder injury group. Likewise, when subgroups were compared, there were no differences in sociodemographic characteristics in laboratory parameters (p>0.05).*

Conclusion: *Attention should be paid to the postoperative consequences of bladder damage during hysterectomy for PAS.*

Key words: *bladder function; placenta accreta spectrum; postpartum hysterectomy*

ÖZET

Amaç: *Plasenta akreta, inkreta ve perkretayı içeren plasenta akreta spektrumu (PAS), anormal bir plasental invazyonu tanımlar. PAS, mesane, üreter ve bağırsak gibi komşu organların artmış mortalite ve morbidite ve yaralanması ile ilişkilidir. Literatürde mesane en sık yaralanan organ olarak bildirilmektedir. Çalışmamızda PAS için yapılan postpartum histerektomi sonrası mesane fonksiyonlarını ve inkontinans sıklığını değerlendirmeyi amaçladık.*

Materyal ve Metot: *Ocak 2016 – Ocak 2018 tarihleri arasında gerçekleştirilen tek merkezli prospektif bir çalışmadır. Elektif sezaryen operasyonu planlanan ve PAS nedeniyle peripartum histerektomi uygulanan toplam 81 hasta dahil edildi. Ulaşılamayan veriler nedeniyle 22 hasta çalışma dışı bırakıldı. Hastalar mesane yaralanması olan (n=20) ve mesane yaralanması olmayan (n=25) olmak üzere iki gruba ayrıldı. Ayrıca mesane yaralanması olan grup ≥2 cm (n=8) ve <2 cm (n=12) olacak şekilde iki alt gruba ayrıldı.*

Bulgular: *İki grup arasında sosyodemografik özellikler arasında istatistiksel olarak anlamlı bir fark yoktu. Laboratuvar parametreleri açısından iki grup arasında anlamlı fark bulunmadı. İlk işeme hissi, normal işeme isteği, mesane boşaltma süresi, maksimum üretral basınç, mesane basıncı, maksimum üretral kapanma basıncı ve rezidüel hacim (p>0,05), güçlü işeme isteği (p>0,05) açısından iki grup arasında anlamlı fark yoktu 439,2±70,05'e karşı 391±67,34, p=0,024) ve maksimum mesane kapasitesi (400,8±65,76'ya karşı 351±57,39, p=0,011) mesane yaralanması grubunda anlamlı olarak daha düşüktü. Aynı şekilde alt gruplar karşılaştırıldığında da laboratuvar parametreleri açısından sosyodemografik özelliklerde farklılık yoktu (p>0,05).*

Sonuç: *PAS için histerektomi sırasında mesane hasarının postoperatif sonuçlarına dikkat edilmelidir.*

Anahtar kelimeler: *mesane yaralanması; plasenta akreata spektrumu; postpartum histerektomi*

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Introduction

The placenta accreta spectrum (PAS), which includes placenta accreta, increta, and percreta, defines an abnormal placental invasion. Placenta accreta and increta are used for superficial and deep myometrial invasion, respectively, while placenta percreta is used for full-thickness myometrial invasion and serosa or adjacent visceral organ inolvement[1,2]. However, the incidence of PAS was 0.8/1000 in 1980; it recently reached 3/1000 (Helena c. Bary-tels, placenta accreta spectrum). In this spectrum, the frequency of placenta accreta was reported to be 79%, increta 14%, and percreta 71.2%.

The main risk factors of PAS are advanced maternal age, increased parity, presence of placenta previa, and previous uterine surgery or curettage[3–5]. PAS is associated with increased mortality and morbidity, disseminated intravascular coagulopathy, renal failure, acute respiratory distress syndrome, infection, increased hysterectomy rates, and injury of adjacent organs such as bladder, ureter, and bowel[1].

The most common approach in the treatment of PAS is hysterectomy. Unfortunately, the urinary tract injury rates reach nearly 29% for hysterectomies performed for PAS, whereas it is 4.8% for standard hysterectomy[6,7]. The bladder is the most common injured organ in the literature. In studies evaluating the incidence of bladder injury in patients who underwent a peripartum hysterectomy, Kayayalcin et al. reported the bladder injury rates as 5.4%, and Yucel et al. reported this rate as 8.88%. Hence, early diagnosis, determining the invasion depth preoperatively, and multidisciplinary surgical team approach including urology team is crucial for cases of urinary tract invasion. Urinary incontinence is a common health issue affecting the quality of life of a woman. Clinical symptoms of urinary incontinence are only seen in 25% of patients who have bladder injury during obstetric and gynecologic surgery[4].

To the best of our knowledge, there is no study evaluating the incidence of urinary incontinence after postpartum hysterectomy in the Turkish population. Our study aimed to assess the urodynamics alterations and frequency of urinary incontinence after postpartum hysterectomy performed for PAS.

Material and Methods

This single-centered prospective study was performed at the University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Obstetrics and Gynecology Department, between January 2016 and January 2018. The local ethics committee approved it of our university, and it was by the principles of the Declaration of Helsinki (2011-KAEK-25 2018/10–12). Written informed consent was obtained from all participants.

A total of 187 patients, who were planned for an elective cesarean section and underwent peripartum hysterectomy due to PAS, were included. The patients were divided into two groups: patients with bladder injury and patients without bladder injury. Furthermore, the bladder injury group was subdivided into two subgroups: bladder injury ≥2 cm and bladder injury <2 cm. During the surgery, the location of bladder injury was not in the trigon part of the bladder in any patient. Therefore, no description has been made regarding the location of the bladder injury. The study was designed based on the size of the bladder injury. Patients with and without bladder injury were compared in bio demographic, intraoperative, postoperative characteristics, laboratory parameters, voiding diary, and urodynamic parameters.

Study Protocol

Patients with PAS are scheduled for elective cesarean section at 36–37th weeks of gestation in our clinic. In the preoperative period, two erythrocyte suspensions and fresh frozen plasma are reserved for patients with hemoglobin values >10 g/dL. In contrast, four units of erythrocyte suspension and fresh frozen plasma are reserved for patients with hemoglobin <10 g/dL. Patients are operated in a lithotomy position. Considering the clinical and sonography findings obtained in the preoperative period, midline or Phannenstiel incision was preferred for the abdominal entrance route. The baby is delivered by making a fundal incision to the uterus, and without removing the placenta, a hysterectomy is performed. Patients with bladder damage during hysterectomy are consulted with the urology department, and control cystoscopy is performed at the end of the surgery. Some measures have been taken to prevent bladder injury. Foley catheter was inserted in all patients in the preoperative period. During the uterine artery dissection, care was taken not to separate the bladder excessively. While performing vesicouterine cavity dissection, sharp dissection (with scissors) was avoided in order not to increase the possibility of bladder injury. The two-fold

repair was performed with 3–0 atraumatic chromic catgut when bladder injury occurred. Patients with bladder injury were routinely followed up with foley catheter for 7–10 days postoperatively[9,10]. Cellulitis or infection appears as a complication in cases where bladder injury is noticed late. Therefore, cystoscopy is routinely recommended if bladder injury is suspected. It is known that the factors causing bladder injury are related to the patients' previous uterine surgery and the increasing invasion of the placenta to the bladder caused by PAS. In the study, the greater the degree of invasion, the greater the bladder injury was seen. In the 6th postoperative month, these patients are called for control, their urination functions are questioned, and urodynamic studies are performed. If bladder and urethral injuries occur, routine intraoperative ureteroscopy is recommended[11,12]. All patients were evaluated for urinary tract infection; appropriate treatment was applied to the patients with infection. In addition, each patient was asked to complete the voiding diary for three days.

Urodynamics; It is a diagnostic method used to reveal or exclude components associated with lower urinary system disorders, to predict the effects of LUT functions and disorders on the upper urinary system, to follow the results of the intervention or treatment performed on the patient, and to investigate the causes of failure of the previous treatments[13]. Independent of urinary incontinence, evaluation of lower urinary system functions of urinary incontinence.

Uroflowmetry is a test in which the amount of urine voided per unit time is measured in ml/sec. Tests in which voiding less than 50% of the total functional bladder capacity is performed are not diagnostic. Since the same patient can void at different volumes during each uroflowmetry measurement, it is impossible to accurately measure the patient's bladder capacity change by uroflowmetric evaluation.

Bladder storage function is evaluated during the urodynamic examination, taking into account the bladder sensation, detrusor activity, bladder compliance, and bladder capacity parameters[14].

Considering the above reasons, the urodynamic study was preferred instead of uroflowmetry to evaluate lower urinary system functions more accurately.

In urodynamic evaluation, the patient is told to empty her bladder before urodynamic, and the remaining volume is measured. Following this, an isotonic NaCl was infused at a rate of 50 ml/min using a disposable double-lumen 8F bladder catheter for filling cystometry in a standard gynecological lithotomy position. The presence of detrusor contractions exceeding 15 cmH2O and can not be inhibited during filling is defined as detrusor instability. The bladder is filled, and the first sense to void (ml), normal desire to void (ml), strong desire to void (ml), and maximum bladder capacity (ml) are recorded. In addition, starting from 100 cc, the patient is coughed for every 100 cc increment to obtain any urine leakage. Valsalva leak point pressure is measured in patients with urine leakage, and pressure greater than 200 cmH20 is accepted as a normal urodynamic study. Maximum urethral pressure is measured when the bladder catheter is withdrawn. Following cystometry, while the bladder is full, the infusion lumen is pumped with liquid, and the catheter is pulled from the catheter to the distal, proximal urethra. This way, maximum urethral closure pressure, and functional urethral length are measured.

Age, gravida, parity, abortion, curettage, height, weight, number of previous cesarean section, presence of prior myomectomy, gestational age at delivery, birth weight, type of incision, method of anesthesia, need for perioperative transfusion, duration of hospitalization, urinary catheterization length, maternal complications and preoperative and postoperative laboratory parameters such as complete blood count, fasting glucose, kidney, and liver function test parameters were recorded. Moreover, patients were questioned for urinary incontinence and first sense to void, normal desire to void, strong desire to void, maximum bladder capacity, bladder emptying time, maximum urethral pressure, bladder pressure, maximum urethral closure pressure, and residual volume parameters were obtained from the urodynamic studies.

Statistical Analysis

Statistical analysis of the study was carried out with SPSS 21.0 program. Power analysis was used to determine the sample size of the study. Considering the power as 80%, the minimum number of patients was calculated with a 30% difference, and the 0.05 p-value was calculated as 20 for each group. The Shapiro Wilk test was used to determine whether the data was normally distributed or not. Data were expressed as mean ± standard deviation, median, or percentage. Student-t-test was used to compare the normally distributed

data between the two groups, and Mann Whitney-U test was used to compare the non-normally distributed data. Chi-square or Fischer Exact test was used to compare categorical variables. P<0.05 value was considered as statistically significant.

Results

A total of 187 patients who were planned for an elective cesarean section and underwent peripartum hysterectomy due to PAS were included. But 81 of these patients whose pathology result was evaluated as PAS were included in the study. A total of 22 patients were excluded because of unavailable data, four patients with morbid obesity, six patients who have pre-operative urinary incontinence and bladder function disorder, one patient with a history of urinary incontinence surgery, and three patients having a history of urinary incontinence before pregnancy are excluded. Since morbid obesity is a risk factor for urinary incontinence, four morbid obesity patients were excluded from the study. Finally, a total of 45 patients were analyzed in the study. The patients were divided into two groups: patients with bladder injury (n=20) and those without bladder injury (n=25). Furthermore, the bladder injury group was subdivided into two subgroups as bladder injury ≥2 cm (n=8) and bladder injury <2 cm (n=12).

None of the patients had urinary incontinence six months after the hysterectomy due to PAS; the two alterations statistically significant in the urodynamic study were "the maximum bladder capacity and strong desire to void. However, we found no difference in these parameters in comparison to subgroups.

The mean age of the patients was 33.87±4.89 years. Patients were divided into two groups: patients with bladder damage (n=20) and those without bladder damage (n=25). The sociodemographic characteristics of all patients are demonstrated in Table 1. There was no statistically significant difference between the two groups regarding age, gravida, parity, abortion, number of curettages, body mass index, number of previous cesarean sections, and presence of prior myomectomy (p>0.05).

Perioperative features of patients with and without bladder injury are shown in Table 2. There was no statistically significant difference between the two groups according to birth weight, perioperative transfusion unit, anesthesia method, and maternal complication rate. Gestational age at delivery was earlier (34 (30–37) vs 36 (28–37), p=0.008), the incision type was preferred to the midline (75% vs 36%, p=0.009), hospital stay (9.5±4.17 vs 6.76±2.11, p=0.014) and urinary catheterization time (7.1±2.22 vs 1.64±1.44, p<0.001) were longer in bladder injury group.

None of our patients had clinical bladder dysfunction symptoms in the postoperative period, and there was no significant difference in the voiding diary. (p=0.863)

Laboratory parameters of patients with and without bladder injury are presented in Table 3. There was no significant difference between the two groups regarding preoperative hemoglobin, preoperative and postoperative platelet, aspartate aminotransferase, alanine aminotransferase, glucose, urea, and creatinine values. Postoperative hemoglobin levels were statistically lower in the bladder injury group (9.25±1.04 vs. 8.41±1.65, p=0.007).

It was technically not possible to statistically compare the voiding diaries of different patients with each other. Therefore, nocturia, which may be one of the most important indicators of a decrease in bladder capacity, was taken as the primary evaluation criterion in evaluating voiding diaries. When the urination diaries were assessed, it was found that no patient woke up more than once at night, and no significant difference was found between the groups in the statistical evaluation made on this issue (p=0.768).

Although a standard test was not used in the verbal interrogation of the patients, the obstructive and irritative symptoms of the bladder were asked together. In this questioning, all of the patients answered no to whether you have urinary incontinence.

The urodynamic properties of patients with and without bladder injury are shown in Table 4. There was no significant difference between the two groups according to the first sense to void, normal desire to void, bladder emptying time, maximum urethral pressure, bladder pressure, maximum urethral closure pressure, and residual volume (p>0.05) while strong desire to void (439.2±70.05 vs. 391±67.34, p=0.024) and maximum bladder capacity (400.8±65.76 vs. 351±57.39, p=0.011) were significantly lower in bladder injury group.

Patients with bladder injury were divided into two subgroups as injury ≥2 cm (n=8) and injury <2 cm (n=12), depending on the extent of the damage. The sociodemographic characteristics of patients with

Table 1. *Sociodemographic characteristics of patients*

	Bladder injury (n=20)	No bladder injury (n=25)	p
Age (year)	34±4.65	33.76±5.18	0.872
Gravida (n)	4 (2–9)	4 (2–11)	0.953
Parity (n)	2 (1–7)	2 (1–10)	0.943
Abortion (n)	0 (0–2)	0 (0–3)	0.491
Curettage (n,%)	1 (5%)	1 (4%)	0.872
Body mass index (kg/m²)	25.64±2.17	25.08±2.06	0.384
Number of previous cessarean section (n)	2 (1–7)	2 (1–4)	0.062
Presence of previous myomectomy (n,%)	4 (20%)	2 (8%)	0.872

Table 2. *Perioperative features of patients with and without bladder injury*

	Bladder injury (n=20)	No bladder injury (n=25)	p
Gestational age at delivery (week)	34 (30–37)	36 (28–37)	**0.008**
Birth weight (grams)	2425.5±413.07	2620.8±299.3	0.073
Perioperative transfusion (unit)	4 (0–15)	4 (0–9)	0.870
Incision – Phannenstiel (n,%) – Midline (n,%)	 5 (25%) 15 (75%)	 16 (64%) 9 (36%)	 **0.009**
Anesthesia – General-anesthesia (n,%) – Spinal anesthesia (n,%)	 17 (85%) 3 (15%)	 17 (68%) 8 (32%)	 0.187
Maternal complication (n,%)	4 (20%)	1 (20%)	0.09
Hospital stay (day)	9.5±4.17	6.76±2.11	**0.014**
Urinary catheterization time (days)	7.1±2.22	1.64±1.44	**<0.001**

Table 3. *Laboratory parameters of patients with and without bladder injury*

	Bladder Injury (n=20)	No Bladder Injury (n=25)	p
Preoperative hemoglobin (g/dl)	9.53±1.57	9.59±1.16	0.870
Postoperative hemoglobin (g/dl)	8.41±1.65	9.25±1.04	**0.007**
Preoperative platelet (/mm³)	244200±70137.2	239720±82709.6	0.848
Postoperative platelet (/mm³)	222000±105139	206200±79839.9	0.784
Preoperative AST (IU/L)	23.25±9.82	25.76±12.58	0.493
Postoperative AST (IU/L)	26.15±8.85	29.2±12.08	0.464
Preoperative ALT (IU/L)	17.35±5.87	19.72±9.4	0.507
Postoperative ALT (IU/L)	19.25±5.99	21.4±13.76	0.855
Preoperative glucose (mg/dl)	83.21±11.41	82.24±11.16	0.792
Postoperative glucose (mg/dl)	85.29±7.53	83.65±7.95	0.486
Preoperative urea (mg/dl)	10.97±7.07	9.71±3.59	0.385
Postoperative urea (mg/dl)	11.92±7.77	10.54±4.53	0.689
Preoperative creatinine (mg/dl)	0.74±0.37	0.58±0.11	0.483
Postoperative creatinine (mg/dl)	0.77±0.42	0.63±0.31	0.138

ALT, alanine aminotranferase; AST, aspartate aminotransferase.

Table 4. *Urodynamic properties of patients with and without bladder injury*

	Bladder Injury (n=20)	No Bladder Injury (n=25)	p
First sense to void (ml)	128.25±15.67	135.9±18.18	0.149
Normal desire to void (ml)	248±38.06	257.8±37.22	0.390
Strong desire to void (ml)	391±67.34	439.2±70.05	**0.024**
Maximum bladder capacity (ml)	351±57.39	400.8±65.76	**0.011**
Bladder emptying time (sn)	19.6±1.54	18.92±1.38	0.200
Maximum urethral pressure (cmH_2O)	122.75±6.97	125.2±6.69	0.283
Bladder pressure (cmH_2O)	85.5±3.59	87.4±5.23	0.158
Maximum urethral closure pressure (cmH_2O)	35.05±5.47	37.2±5	0.176
Residual volume (ml)	45±8.43	43.2±7.05	0.409

bladder injury ≥2 cm and <2 cm were presented in Table 5. There was no significant difference between the two groups about age, gravida, parity, abortion, number of curettages, body mass index, number of previous cesarean sections, and presence of prior myomectomy (p>0.05).

Perioperative features of patients with bladder injury ≥2 cm and <2 cm were demonstrated in Table 6. No statistically significant differences were found between the two groups regarding gestational age at delivery, birth weight, perioperative transfusion unit, incision type, anesthesia method, maternal complication rate, length of hospital stay, and urinary catheterization time (p>0.05).

Laboratory parameters of patients with bladder injury ≥2 cm and <2 cm were presented in Table 7. There was no significant difference between the two groups regarding preoperative and postoperative platelet, aspartate aminotransferase, alanine aminotransferase, glucose, urea, and creatinine values. In contrast, preoperative and postoperative hemoglobin levels differed significantly between the two groups (p=0.013 and p=0.041).

Urodynamic properties of patients with bladder injury ≥2 cm and <2 cm were shown in Table 8. There was no statistically significant difference between the two groups according to the first sense to void, normal desire to void, strong desire to void, maximum bladder capacity, bladder emptying time, maximum urethral pressure, bladder pressure, maximum urethral closure pressure, and residual volume (p>0.05).

Discussion

Since the incidence of PAS has recently increased, both obstetricians and urologists have started to come across PAS complications. Adjacent organ injury is an important concern for peripartum hysterectomies performed for PAS. Bladder adherent to the uterus due to prior surgery and increased blood flow due to the invasion of the bladder by the placenta are the most common reasons for bladder injury and massive hemorrhage. In cases with bladder invasion, it is known that maternal mortality, massive bleeding, infection, and morbidity secondary to adjacent organ injury are increased[15]. In the literatüre, the bladder injury rate during cesarean section was reported as 0.08–0.94%, while it was 14.3% during hysterectomy. This rate was reported by Yasa et al. as 30.5% in PAS cases with bladder invasion. t-testSimilarly, Norris et al. claimed that this rate is 36.1%, while Tam et al. showed it as 22.1% in PAS cases[16,17]. Our study found the bladder injury rate as 44%, which is higher than the literature. This increased rate could be related to the number of prior uterine surgery that can lead to adhesion between the uterus and bladder in our patients. Being a reference hospital in our region and operating complex cases could explain this increasement.

Generally, the midline incision is preferred for optimal exploration in PAS cases. In our study, a midline incision was statistically more common in bladder injury cases which are expected to be more complicated. Moreover, hospital stay and catheterization length were longer in bladder injury cases in our study. In cases of bladder injury, the urinary catheter is routinely followed for 7–10 days without removing the urinary catheter.

Most of the studies in the literature investigated the presence of bladder damage in cases of PAS. Still, no study evaluates how bladder functions are affected among these groups. Our study evaluates whether there is a difference between the groups with and without bladder injury in the urodynamic examination. In addition, we investigated the bladder functions of patients with bladder injury according to the degree of injury in the urodynamic test. In our study, when the urodynamic properties of the group with and without bladder injury were compared, a significant difference was found in terms of maximum bladder capacity and a strong desire to void. However, we found no difference in these parameters in comparison of subgroups. The presence or absence of bladder injury in patients with PAS does not differentiate bladder function between patients in the postoperative period.

When the studies in the literature are examined, it has been stated that bladder injury during PAS operations is a complication. However, there is no study showing the bladder function of the patients with bladder injury during the postoperative period in these studies. The greatest strength was verifying urinary incontinence and urodynamic alterations six months after hysterectomy due to PAS comparing patients that had or not bladder injury.

Our study's limitations are the low number of patients included in the research and the inability to access the data of 22 patients in our study group. However, PAS cases are rare. In addition, our study population is the largest group that underwent hysterectomy and urodynamics for PAS to the best of our knowledge.

Table 5. *Sociodemographic characteristics of patients with bladder injury ≥2 and <2 centimeters.*

	Bladder Injury ≥2 cm (n=8)	Bladder Injury <2 cm (n=12)	P
Age (year)	33.5±5.35	34.33±4.33	0.816
Gravida (n)	2 (2–7)	2 (2–9)	0.969
Parity (n)	2 (1–6)	2 (1–7)	0.937
Abortion (n)	2 (25%)	2 (16.6%)	0.450
Curettage (n,%)	1 (12.5%)	1 (8.3%)	0.402
Body mass index (kg/m²)	25.73±2.73	25.58±1.83	0.969
Number of previous cessarean section (n)	2 (1–5)	2 (1–7)	0.322
Presence of previous myomectomy (n,%)	1 (12.5%)	3 (25%)	0.494

Table 6. *Perioperative features of patients with bladder injury ≥2 and <2 centimeters*

	Bladder Injury ≥2 cm (n=8)	Bladder Injury <2 cm (n=12)	P
Gestational age at delivery (week)	34 (31–37)	34 (30–37)	0.839
Birth weight (grams)	2430±538.97	2422.5±331.42	0.969
Perioperative transfusion (unit)	4 (0–7)	4 (0–15)	0.111
Incision			
– Phannenstiel (n,%)	1 (12.5%)	4 (33.3%)	0.292
– Midline (n,%)	7 (87.5%)	8 (66.7%)	
Anesthesia			
– General-anesthesia (n,%)	8 (100%)	4 (33.3%)	0.135
– Spinal anesthesia (n,%)	0 (0%)	8 (66.7%)	
Maternal complication (n,%)	1 (12.5%)	3 (25%)	0.505
Hospital stay (day)	9.63±3.89	9.42±4.52	0.938
Urinary catheterization time (days)	7.63±2.13	6.75±2.3	0.395

Table 7. *Laboratory parameters of patients with bladder injury ≥2 and <2 centimeters*

	Bladder Injury ≥2 cm (n=8)	Bladder Injury <2 cm (n=12)	P
Preoperative hemoglobin (g/dl)	10.61±1.52	8.8±1.16	**0.013**
Postoperative hemoglobin (g/dl)	9.44±2	7.73±0.93	**0.041**
Preoperative platelet (/mm³)	221250±44187.1	259500±81338.24	0.396
Postoperative platelet (/mm³)	186875±64687	245416.6±122210.3	0.396
Preoperative AST (IU/L)	25.63±11.16	21.67±8.98	0.395
Postoperative AST (IU/L)	24.13±6.77	27.5±10.06	0.587
Preoperative ALT (IU/L)	15.88±2.03	18.33±7.36	0.786
Postoperative ALT (IU/L)	18.63±6.55	19.67±5.85	0.536
Preoperative glucose (mg/dl)	79.75±5.99	85.51±13.70	0.436
Postoperative glucose (mg/dl)	81.88±5.54	87.57±8.02	0.069
Preoperative urea (mg/dl)	12.52±5.81	9.93±7.86	0.153
Postoperative urea (mg/dl)	12.96±7.02	11.22±8.45	0.487
Preoperative creatinine (mg/dl)	0.71±0.42	0.76±0.35	0.666
Postoperative creatinine (mg/dl)	0.75±0.55	0.78±0.33	0.063

ALT, alanine aminotranferase; AST, aspartate aminotransferase.

Table 8. *Urodynamic properties of patients with bladder injury ≥2 and <2 centimeters*

	Bladder Injury ≥2 cm (n=8)	Bladder Injury <2 cm (n=12)	p
First sense to void (ml)	126.25±22.48	129.58±9.8	0.172
Normal desire to void (ml)	245±45.36	250±34.38	0.727
Strong desire to void (ml)	370±50.71	405±75.26	0.246
Maximum bladder capacity (ml)	346.25±59.27	354.17±58.54	0.615
Bladder emptying time (sn)	19.75±1.58	19.5±1.57	0.692
Maximum urethral pressure (cmH_2O)	124.38±7.76	121.67±6.51	0.363
Bladder pressure (cmH_2O)	83.75±2.31	86.67±3.89	0.069
Maximum urethral closure pressure (cmH_2O)	37.38±5.10	33.33±5.52	0.088
Residual volume (ml)	45.63±9.43	44.58±8.11	0.875

Conclusion

Attention should be paid to the postoperative consequences of bladder damage during hysterectomy for PAS.

Conflict of Interest

The authors report no declarations of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Platelet-Lymphocyte Ratio As a Novel Predictor of Severity in Patients With Unstable Angina Pectoris: Randomized Control Double-Blind Study

Kararsız Angina Pektorisli Hastalarda Ciddiyetin Yeni Bir Belirteci Olarak Trombosit Lenfosit Oranı: Randomize Kontrollü Çift Kör Çalışma

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ABSTRACT

Aim: *Acute Coronary Syndrome (ACS); covers a wide spectrum of clinical conditions ranging from Non-ST and ST-Elevation Myocardial Infarction to unstable angina pectoris (UAP). UAP does not show detectable with any biomarkers in the Emergency Department (ED). Platelet-lymphocyte ratio (PLR) has been introduced as a potential marker to determine excess thrombotic activity and inflammation in cardiac disorders. Syntax score (SXscore) is an anatomic scoring system based on coronary angiography that quantifies lesion severity and complexity and predicts poor cardiovascular outcomes, including mortality, in patients with ACS. This study aimed to investigate the predictive value of PLR compared with SXscore in patients with UAP in the ED.*

Material and Method: *The study group consisted of patients diagnosed with UAP who presented in ED and adult patients who experienced UAP in ED. The control group was comprised of healthy adults with no chronic disease. We performed CA to the patients suspected ACS in the study group, and the Syntax Score was calculated for each patient. The levels of PLR were compared between the study and control group, and PLR levels of the study group were compared with Syntax scores of the former group.*

Results: *The mean levels of PLR were 122.89±52.44 in the UAP group and 104.21±22.85 in the control group (p: 0.005). The PLR level of 113.98 had a sensitivity of 55.8%, specificity of 66.7% and was negatively correlated with SXscore (r=-0.325; p: 0.004).*

Conclusion: *PLR levels significantly increase in patients presenting with UAP. PLR may be considered a novel marker in predicting the severity of UAP. However, it was found to be ineffective in evaluating coronary vascular damage.*

Key words: *syntax score; platelet-lymphocyte ratio; unstable angina pectoris*

ÖZET

Amaç: *Akut Koroner Sendrom (AKS), ST segment yükselmeli miyokard enfarktüsünden kararsız angina pektorise (UAP) kadar geniş bir klinik durum yelpazesini kapsar. UAP, Acil Servis kliniğinde herhangi bir biyobelirteçle tespit edilemez. Trombosit lenfosit oranı (PLR), kardiyak bozukluklarda aşırı trombotik aktiviteyi ve enflamasyonu belirlemek için potansiyel bir işaret olarak gösterilmiştir. Syntax skoru (SXscore), sadece lezyon şiddetini ve kompleksitesini ölçmekle kalmayan, aynı zamanda AKS'li hastalarda mortalite dahil olmak üzere agır kardiyovasküler sonuçları öngören koroner anjiyografiye dayalı anatomik bir skorlama sistemidir. Bu çalışmanın amacı, UAP'lı hastalarda trombosit lenfosit oranı ile SXscore karşılaştırılarak bu hastalarda PLR'nin prediktif değerini ortaya koymaktır.*

Materyal ve Metot: *Çalışma grubu, acil servise başvuran UAP tanısı alan hastalar ve acil servise'de UAP tanıs alan yetişkin hastalardan oluşturuldu. Kontrol grubu, kronik hastalığı olmayan sağlıklı yetişkinlerden oluşmuştur. Çalışma grubunda AKS şüphesi olan hastalara koroner anjiografi uyguladık ve her hasta için Syntax Skoru hesaplandı. Çalışma ve kontrol grubu arasında PLR seviyeleri karşılaştırıldı ve çalışma grubunun PLR seviyeleri ile Syntax skorları karşılaştırıldı.*

Bulgular: *Ortalama PLR düzeyleri UAP grubunda 122,89±52,44 ve kontrol grubunda 104,21±22,85 idi (p: 0,005). PLR düzeyi 113,98 olduğunda %55,8 duyarlılığa, %66,7 özgülüğe sahip olarak bulundu ve SXscore ile negatif korelasyon gösterdiği görülüldü (r=-0,325; p: 0,004).*

Sonuç: *UAP ile başvuran hastalarda PLR seviyelerinin önemli ölçüde arttığı görüldü. PLR, UAP'ın ciddiyetinin tahmininde yeni bir belirteç olarak düşünülebilir. Ancak koroner vasküler hasarın değerlendirilmesinde etkisiz olduğu görülmüştür.*

Anahtar kelimeler: *syntax score; platelet-lymphocyte oranı; unstable angina pektoris*

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Introduction

Acute Coronary Syndrome (ACS) is the primary cause of death in the world[1]. The chest pain covers almost 6.3% of the Emergency Department (ED)[2]. ACS; covers a wide spectrum of clinical conditions ranging from unstable angina pectoris (UAP) to Non-ST Elevation Myocardial Infarction (N-STEMI) and ST-Elevation Myocardial Infarction (STEMI). UAP is thought to be an ACS in which there are no detectable cardiac biomarkers of myocardial necrosis such as creatine-kinase MB isozyme, troponin, myoglobin in the circulation[3].

Missed UAP patients are challenging because of various clinical manifestations[4]. Missed Myocardial Infarction is still one of the most common reasons behind malpractice lawsuits against emergency physicians, almost 20% of all claims[5]. All chest pain patients <25% will have an ACS[6]. If patients at high risk for ACS could be recognized promptly, it has the potential to reduce mortality, morbidity, and adverse effects of delayed treatment[7]. Therefore, accurate and fast risk stratification is paramount in the acute management of these patients, mainly to identify those patients with immediate risk of complications, as those with an ACS.

The Syntax score (SXscore) is an anatomic scoring system based on coronary angiography (CA) designed to be performed by the cardiologist that not only quantifies lesion severity and complexity but also predicts poor cardiovascular outcomes, including mortality, in patients with ACS[8,9]. The SXscore can predict mortality and morbidity at early and late follow-up in patients irrespective of disease severity in different clinical situations, including ACS. In the PCI study, Capodanno et al.[9] reported, Patients were divided into tertiles based on SYNTAX scores: low (≤18), intermediate (>18 to 27), and high (>27). At 1 year, patients in the highest tertile showed a significantly higher mortality (13.1% vs. 2.5%, P<0.001) and MACE rate (21.4% vs. 7.4%, P<0.001) than patients in the lowest tertile[10].

Early diagnosis and the initiation of appropriate treatment within 24 hours are essential to reduce UAP-related mortality and morbidity[11]. Despite the investigated use of various diagnostic, prognostic and predictive factors, there is currently no biomarker, such as troponin, etc., in patients with UAP. There is still a need for a sensitive, specific, simple, and predictive marker in patients with UAP to reduce mortality and provide a good outcome with cost-effective treatments.

The platelet-lymphocyte ratio (PLR) has been claimed to have the potential as a marker to help identify thrombotic activity and inflammation in cardiac diseases[12]. Inflammatory mediators and endothelial dysfunction play a fundamental role in the pathophysiology of ACS and widespread coronary inflammation found during UAP[13]. It has recently been observed that there is a close relation between cardiovascular mortality and the number of platelets or their ability to aggregate. Platelets play a key role in the pathophysiology of ACS. Compounded with fibrin, platelets form a coronary thrombus[14]. The PLR, which is calculated by dividing absolute platelet count by absolute lymphocyte count, is a new indicator of the inflammatory response. However, recent studies have shown that PLR, which is evaluated as a prognostic marker of ACS, may also increase in patients with N-STEMI and STEMI[15–17].

However, there are no studies in the literature regarding PLR levels in patients with UAP. No studies in the literature have examined PLR levels compared with SXscore in patients with UAP in the ED. The present study aimed to investigate the predictive value of PLR levels compared with SXscore in patients with UAP in the ED.

Methods

Medipol University Clinical Research Ethics Committee approved this prospective randomized controlled study. The study was conducted in Medipol University Hospital Adult ED and Cardiology Department within 12 months of approval. (20.01.2016/E.1049-30)

Study and Control Groups

The study group consisted of patients diagnosed with UAP who presented in ED and adult patients who experienced UAP in ED. UAP was defined according to Thygesen K et al.'s Third universal definition of myocardial infarction[3]. The control group was comprised of healthy adults with no chronic disease. Patients who agreed to participate in the study provided a written informed consent form. All patients in both groups were ≥18 years old. The groups were named 'UAP' and 'Control.' Gender, Age, hemograms, and PLR levels were recorded for both groups. The study group examined the following: Blood Urea Nitrogen (BUN), creatinine, CK-MB, 0. and 3. Hour cTnI and Syntax score. We performed CA to the patients suspected ACS in the

study group, and the Syntax Score was calculated for each patient. The levels of PLR were compared between the study and control group, and PLR levels of the study group were compared with Syntax scores of the former group. The cardiologist performed coronary angiography cardiologists interpreted degrees of coronary artery stenosis are separated to make the study double-blinded.

Inclusion and Exclusion Criteria

Inclusion Criteria

UAP group: Patients presented with suggestive of UAP above the age of 18 without known previous history of CAD were enrolled in the study.

Control group: The control group consists of healthy adults above 18 with no chronic disease.

Exclusion Criteria

Patients were also excluded if they had a previously known disease to explain the chest pain other than angina and did not agree to participate in the study.

Biochemical Analysis

All blood samples were taken from the brachial veins. BUN and creatinine were measured with an autoanalyzer (Cobas6000, Roche, Tokyo, Japan). Blood samples for hemograms were collected in 2 ml EDTA tubes and analyzed on an automated hematology analyzer (XT-2000I; Symex, Osaka, Japan). The PLR was calculated as the ratio of platelet count to lymphocyte count. Blood samples were centrifuged within 30 minutes, and CK-MB, 0th and 3rd hour cardiac troponin-I (cTnI) were determined with AQT90 FLEX analyzer device (Radiometer, Copenhagen, Denmark) by immunoassay method. Cut-off values for CK-MB and cTnI were 7.2μg/L and 0.023μg/L, respectively.

Coronary Angiography and Syntax Score

The cardiologist performed coronary angiography through right femoral catheterization on patients with exertional dyspnea symptoms, chest pain, and without ST-segment and T wave changes (ECG). Blinded experienced interventional cardiologists interpreted degrees of coronary artery stenosis. A syntax scoring system was used to assess angiographic vessel-specific disease severity[18].

Statistical Analysis

Statistical analyses were made using commercial statistical software (SPSS Ver. 23.0, IBM Inc., Chicago, IL, USA). Variables were stated as mean and standard deviation. Frequencies were compared with the Chi-square and Fisher's exact tests. Spearman's correlation tests were applied for correlation analyses. Simple correlation analyses were performed to investigate the association of serum PLR levels with SX scores. To determine a cut-off value of PLR level for UAP, receiver operating characteristic (ROC) analysis was performed in sensitivity and specificity calculations. A value of $p<.05$ was considered statistically significant.

Results

The study included 77 patients admitted with UAP and 75 control subjects. The mean age was 64.23±11.02 years in the study group and 65.36±10.35 years in the control group (p=0.51). The study group comprised 28 (36%) females and 49 (64%) males and the control group, 28 (37%) females and 47 (63%) males (p=. 90). In the UAP group, all troponin and CK-MB values were negative. The mean levels of platelet were 241.30±53.68 10^3/μL and lymphocyte were 2.22±0.81 10^3/μL in the study group. The mean levels of platelet were 220.44±40.13 10^3/μL, and lymphocyte was 2.18±0.48 10^3/μL in the control group. The mean levels of PLR of the UAP group (122.89±52.44) were higher than those of the control group (104.21±22.85) (Fig. 1, p: 0.005). The area under the ROC curve for the PLR level was 0.597 (95% confidence interval [CI], 0.503–0.690), the PLR level had a sensitivity of 55.8% and specificity of 66.7% at 113.98 (Fig. 2). PLR levels were found negatively correlated with SXscore in the study (r=-0.325; p: 0.004) (Fig. 3).

Discussion

Several factors in cardiac diseases that could lead to predicting in previous studies have been analyzed. However, no studies in the literature have examined PLR levels compared with SXscore to predict the severity of coronary pathology in patients with UAP in the ED.

Most commonly caused by atherosclerosis, ACS is the leading cause of death worldwide. Atherosclerosis is a systemic, lipid-driven immune inflammatory disease[14]. ACS is an inflammatory disease, and serum levels of inflammatory markers, such as interleukin (IL)-6, IL-18, and C-reactive protein, evaluate patients with

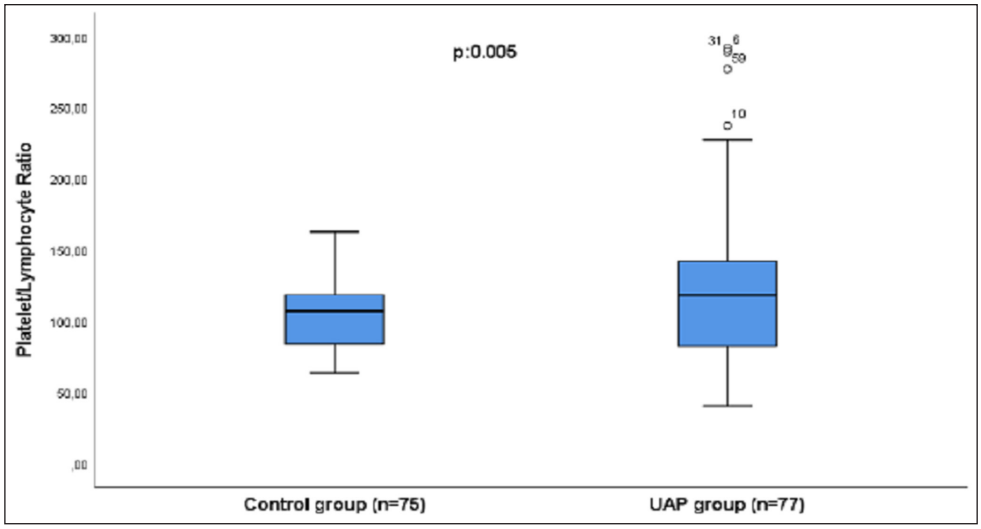

Figure 1. *Comparison of PLRs between groups.*

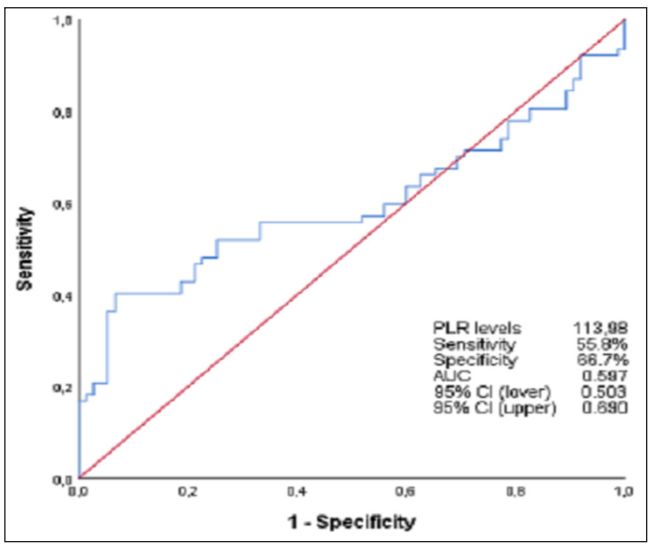

Figure 2. *Receiver-operating characteristic analysis of PLR levels for each group (AUC, area under the curve).*

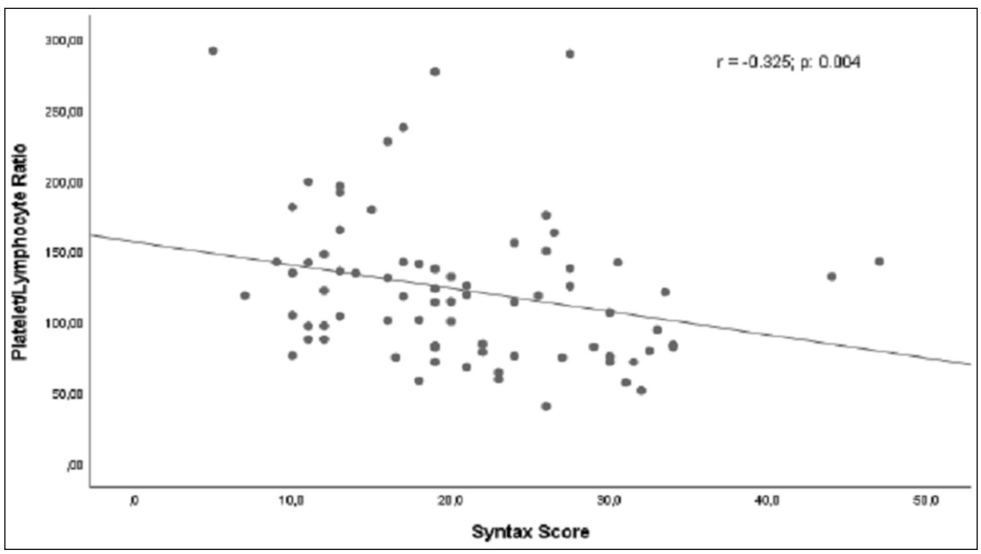

Figure 3. *Correlation between PLR and Syntax score.*

CAD[19]. The inflammation leading to ACS encourages research into the clinical usage of new inflammatory biomarkers. (17). Eight to 10 million individuals are evaluated annually in the EDs in the United States (US) for possible acute MI[20]. Many of these individuals are assessed with serial cardiac markers and held in observation units for stress testing or cardiac imaging, which is time-consuming and costly. In patients with UAP, the troponin values and repeats are negative, and no detectable blood test is available in the diagnosis of UAP in the ED[21].

Predicting coronary anatomy as early as possible will provide precious information about the major adverse cardiac events (MACE) and risk of cardiac death. The inflammatory processes play a key role in the development of atherosclerosis, destabilization of atherosclerotic plaques, and formation of clots on the plaque surface[22]. Increased platelet activity is closely associated with atherosclerosis and thromboembolic states; ACS increases inflammation in the atherosclerotic plaques within months[23]. It has been suggested that the PLR is a new indicator showing chronic inflammation. In particular, the PLR has been introduced as a potential marker to determine excess thrombotic activity and inflammation in cardiac disorders[24].

A previous study showed the relationship between PLR and coronary collateral development in patients with stable angina pectoris and chronic total occlusion[25]. In another study, the SXscore is an independent predictor of the 1-year rates of death, cardiac death, MI, and target vessel revascularization in patients with N-STEMI who undergo PCI[26], and high preprocedural PLR levels were found to be significant and independent predictors of no-reflow in patients with STEMI[27]. In addition, Kurtul et al. reported; the correlation of PLR with SXscore in patients with ACS, including NSTEMI and STEMI. There was a positive correlation between PLR levels and SXscore in patients with ACS[28]. However, there are no studies in the literature regarding PLR levels in patients with UAP. No studies in the literature have examined PLR levels compared with SXscore in patients with UAP in the ED. In the present study, although there is a significant increase in serum PLR levels in patients with UAP compared to healthy control subjects, PLR levels were negatively correlated to SXscore in patients with UAP, and PLR levels have a high negative link between SXscores in patients with UAP.

This early and simple prediction by a PLR of inflammation is important. It may improve our ability to risk stratify UAP patients and guide therapeutic decisions and preserve the patients from MACE and risk of sudden cardiac death. The study results have shown that PLR is sufficient to expose high values with poorly battered coronary arteries and has a high negative link between SXscores.

This study showed a significant increase in serum PLR levels in patients with UAP compared to healthy control subjects; recent research has already put this assumption forward[29]. What is novel about this study is that the Syntax score, most widely used to predict coronary artery lesion with CA, was negatively correlated to serum PLR levels in patients with UAP. The previous finding can be explained by the fact that the endothelial nitric oxide levels of coronary arteries in the UAP and the coronary anatomy could not be hardly damaged as can be found in non-ST elevation myocardial infarction and ST-elevation myocardial infarction[30].

Conclusion

There is currently no biomarker, such as troponin, etc., to diagnose and predict coronary pathology's severity in patients with UAP in the ED. The PLR may be an important, simple, and cost-effective tool predicting the severity but not the complexity of coronary atherosclerosis in patients with UAP. Thus, the PLR levels can be used for risk stratification in patients with UAP.

Study Limitations

PLR may be affected by several pathological variables. However, it was not possible in this study to control all the variables that could influence PLR levels. The contact time to the hospital was accepted as the initial hour for this study. The period that started after collecting the first blood samples was not standardized in every patient, and the number of subjects included in the study was limited. And also, patients with UAP were reluctant to undergo coronary angiography procedures; this also kept our list short.

Conflict of Interests

The author(s) declare no potential conflict of interest regarding this article's research, authorship, and publication.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Relationship Between Saphenous Vein Graft Disease and Triglyceride Glucose Index

Safen Ven Greft Hastalığı ile Trigliserit Glukoz İndeksi Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Aim: *It is known that insulin resistance, one of the main components of metabolic syndrome, is associated with endothelial dysfunction and related diseases. Insulin resistance can be evaluated by HOMA-IR and indirectly by triglyceride-glucose (tg-glucose) index. We aimed to investigate the relationship between saphenous vein graft disease (SVGD) and tg-glucose index.*

Material and Method: *418 patients who underwent coronary angiography in our clinic between January 2019 and December 2020 and had a history of coronary artery bypass grafts were included retrospectively. The patients were divided into two as those with 50% or more stenosis in at least one of their SVG (SVGD group) and those without (control group). Tg-glucose index was calculated by the formula ln (fasting tg X fasting glucose/2). A value of P<0.05 was considered statistically significant.*

Results: *The mean age of 185 patients in the SVGD group was 67.3±4.3 (25.9% female), and the mean age of 233 patients in the control group was 66.4±8.2 (25.7% female). The ejection fraction values of the patients in the SVGD group were lower than the control group (51.6±9.0% & 55.9±6.5, p<0.001) and serum creatinine, CRP, triglyceride, glucose and tg-glucose index values were higher (p=0.041, p=0.003, p<0.001, p<0.001 and p<0.001, respectively). In multivariate logistic regression analysis, low EF, high serum triglyceride and glucose values and tg-glucose index were found to be associated with SVGD. Pairwise comparison of ROC curve analysis revealed that tg-glucose index had better performance than glucose or triglyceride levels to predict SVGD.*

Conclusion: *Tg-glucose index is a biomarker that can be calculated from routine biochemistry tests and can give better results than serum glucose and triglyceride values in predicting SVGD.*

Key words: *coronary artery bypass; saphenous vein graft; triglyceride-glucose index*

ÖZET

Amaç: *Metabolik sendromun ana bileşenlerinden biri olan insülin direncinin endotel disfonksiyonu ve ilişkili hastalıklar ile bağlantılı olduğu bilinmektedir. İnsülin direnci HOMA-IR ve indirekt olarak da trigliserit-glukoz (tg-glukoz) indeksi ile değerlendirilebilmektedir. Bu çalışmanın amacı, safen ven greft hastalığı (SVGH) ile tg-glukoz indeksi arasındaki ilişkiyi araştırmaktır.*

Materyal ve Metot: *2019–2020 yıllarında kliniğimizde koroner anjiyografi yapılan ve koroner arter bypass greft öyküsü olan 418 hasta çalışmaya retrospektif olarak dahil edildi. Hastalar SVG'lerinden en az birinde %50 veya fazla darlık olanlar (SVGH grubu) ve olmayanlar (kontrol grubu) şeklinde ikiye ayrıldı. Tg-glukoz indeksi ln (açlık tg X açlık glukoz/2) formülü ile hesaplandı. P<0,05 değeri istatistiksel olarak anlamlı kabul edildi.*

Bulgular: *SVGH grubundaki 185 hastanın yaş ortalaması 67,3±4,3 (%25,9 bayan), kontrol grubundaki 233 hastanın yaş ortalaması 66,4±8,2 (%25,7 bayan) idi. SVGH grubundaki hastaların ejeksiyon fraksiyonu değerleri kontrol grubuna göre daha düşükken (%51,6±9,0 & %55,9±6,5, p<0,001); serum kreatinin, CRP, trigliserit, glukoz ve tg-glukoz indeksi değerleri daha yüksekti (sırasıyla; p=0,041, p=0,003, p<0,001, p<0,001 ve p<0,001). Çok değişkenli lojistik regresyon analizinde düşük EF, yüksek serum trigliserit ve glukoz değerleri ile tg-glukoz indeksi SVGH ile ilişkili bulundu. ROC eğrisi analizinin ikili karşılaştırması, tg-glukoz indeksinin SVGH'yi tahmin etmek için glukoz ve trigliserit değerlerine göre daha iyi performansa sahip olduğunu ortaya koydu.*

Sonuç: *Tg-glukoz indeksi rutin biyokimya tetkiklerinden hesaplanabilen, SVGH'nı öngörmede serum glukoz ve trigliserit değerlerinden daha iyi sonuç verebilecek bir biyobelirteçtir.*

Anahtar kelimeler: *koroner arter bypass; safen ven grefti; trigliserit-glukoz indeksi*

Introduction

There are studies showing that chronic inflammatory process is effective in the development of insulin resistance[1–3]. It is known that insulin resistance triggers endothelial dysfunction by increasing oxidative stress and causes dyslipidemia by affecting lipid metabolism[4,5].

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The process consisting of endothelial dysfunction, dyslipidemia and chronic inflammation is the basis of atherosclerosis[6,7]. Therefore, insulin resistance is associated with coronary artery disease both directly and indirectly. Determining whether the host has insulin resistance and its level is also important in terms of the treatment approach. The fact that it is a calculable parameter from laboratory data has made the use of HOMA-IR widespread in daily practice[8,9]. Apart from the HOMA-IR level, the tg-glucose index, which can be calculated using serum triglyceride and glucose levels, can indirectly provide information about insulin resistance[10]. It has been shown to be associated with atherosclerosis better than HOMA-IR[11].

SVGs, which are widely used in coronary artery bypass surgery, can remain less patented than arterial grafts due to the peculiar characteristics of the venous system[12]. It has been shown that 60% of saphenous grafts remained patents after 10 years, and 50% of them had severe stenosis[13]. Thrombosis, intimal hyperplasia and atherosclerosis are involved in the pathogenesis of vein graft disease. While the frequency of thrombosis is high in the early postoperative period, atherosclerosis plays a dominant role in the later period[14]. It is known that insulin resistance is effective in the development of atherosclerosis, and it has been shown that the risk can be reduced with treatments that reduce insulin resistance[15]. The aim of this study is to investigate the relationship between tg-glucose index, which can give information about the insulin resistance, and SVGD.

Material and Methods

418 patients who underwent coronary angiography in our clinic between January 2019 and January 2021 and had a history of coronary artery bypass graft were included in the study. Patients were divided into two groups: those with 50% or more stenosis in at least one of the saphenous vein grafts as the SVGD group, and those without stenosis as the control group. Systolic heart failure, left ventricular ejection fraction <40% ; Hypertension was defined as patients' systolic and diastolic blood pressure >140/90 mmHg or the patient's use of any anti-hypertensive medication. Diabetes mellitus (Type 2 DM) was defined as having a previous diagnosis of DM or using anti-diabetic medication or a fasting blood glucose >126 mg/dL or HbA1 c >6.5%. At least 8-hour fasting venous blood samples were taken from the patients and analyzed using appropriate methods. Routine biochemistry, complete blood values, and lipid profile results were recorded. Tg-glucose index was calculated using the formula ln (fasting tg X fasting glucose/2). Patients with a diagnosis or suspicion of coronavirus-19, hematological disease or malignancy, chronic liver failure, autoimmune disease, and rheumatological disease or incomplete laboratory results were excluded from the study.

The study was approved by the local Clinical Research Ethics Committee of our hospital (20.5.2021/1412) and the study protocol was prepared in accordance with the ethical rules of the 1975 Helsinki Declaration.

Statistical Analysis

All statistical analyses were performed with SPSS 17 (SPSS, Inc., Chicago, Illinois, USA) and MedCalc v. 19.6.1. Continuous variables were exoressed as mean ± standard deviation (mean ± SD) or median (interquartile range); categorical variables were expressed as numbers and percentages. Comparison of continuous variables between groups was performed using t-test and Mann-Whitney U test or the $\chi 2$ test or Fisher's Exact test for categorical variables. Whether the continuous variables had a normal distribution was analyzed using the Shaphiro-Wilk test. Variables with a p value of ≤0.01 in the univariate analysis were included in the multivariate analysis. Results are expressed as relative risk and 95% confidence interval (CI). A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients included in the study was 66.8±6.7 (74.1% male). 185 patients with 50% or more stenosis in at least one of the saphenous vein grafts were included in the SVGD group, and 233 patients without stenosis were included in the control group. There was no statistically significant difference between SVGD group and control group in terms of basal demographic characteristics. The mean ejection fraction values of the patients in the SVGD group were lower than the control group (51.6±9.0% & 55.9±6.5, p<0.001); serum creatinine, CRP, triglyceride, glucose and tg-glucose index values were found to be higher than the control group (p=0.041, p=0.003, p<0.001, p<0.001 and p<0.001, respectively). The demographic characteristics of the patients included in the study and the comparison of laboratory results are summarized in Table 1.

Multivariate regression analysis (Model 1) in which triglyceride, glucose values and other variables were taken and another regression analysis (Model 2) in which triglyceride and glucose values were excluded and other variables were taken with Tg-glucose index were used to analyze variables that could predict SVGD. According to Model 1, low ejection fraction, serum triglyceride and glucose values were found to be predictors for SVGD; In model 2, tg-glucose index and again low ejection fraction were found to be associated with SVGD (Table 2).

Table 1. *Comparison of demographic properties and laboratory results of groups*

	SVGD group (n=185)	Control group (n=233)	p
Age, years	67.3±4.3	66.4±8.2	0.237
Female, n (%)	48 (25.9)	60 (25.7)	0.985
Diabetes Mellitus, %	57	56.8	0.999
Hypertension, %	71.8	73	0.836
ESRD or GFR ≤45 ml/min/1.73 m^2, %	4.2	3.2	0.726
Systolic BP, mm Hg	127.4±17.3	122.9±12.4	0.108
Diastolic BP, mm Hg	78.8±9.7	74.0±8.3	0.497
LVEF, %	51.6±9.0	55.9±6.5	0.001
Hemoglobin, g/dL	13.2±1.8	13.1±1.8	0.646
WBC, 10^3/mL	8.4±2.1	8.5±2.0	0.529
PLT, 10^3/mL	232.2±66.5	238.1±62.2	0.356
Glucose, mg/dL	162.9±71.1	123.2±41.5	<0.001
Urea, mg/dL	42.3±17.6	38.6±14.2	0.186
Creatinine, mg/dL	1.0±0.7	0.9±0.4	0.041
LDL, mg/dL	126.9±35.5	124.8±35.0	0.545
HDL, mg/dL	38.6±8.2	39.2±7.3	0.481
Triglyceride, mg/dL	210.1±105.2	170.1±97.8	<0.001
CRP, median (IQR)	5.6 (14.5)	2.5 (5.6)	0.003
Tg-glucose index	5.1±0.2	4.8±0.2	<0.001
Albumin, g/dL	3.8±0.4	3.8±0.3	0.146
Acetylsalicylic acid,%	80.8	85.7	0.335
Statin, %	62.7	63.4	0.912
Beta blocker, %	86.1	86.5	0.942
ACEI/ARB, %	77.6	69.8	0.195

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CRP, C-reactive protein; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; LVEF, left ventricle ejection fraction; Tg, triglyceride; PLT, platelets; WBC, white blood cell count.

Table 2. *Univariate and multivariate regression analysis*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Glucose	1.013 (1.009–1.017)	<0.001	1.013 (1.006–1.019)	<0.001*
Triglyceride	1.004 (1.002–1.006)	<0.001	1.006 (1.002–1.009)	0.002*
EF	0.933 (0.900–0.968)	<0.001	0.927 (0.888–0.967)	<0.001**
CRP	1.017 (1.017–1.029)	0.004	1.004 (0.980–1.029) –	0.726
Creatinine	1.646 (1.067–2.539)	0.024		
Tg-glucose index	25.03 (10.77–58.13)	<0.001	48.86 (14.05–169.91)	<0.001**

CRP, C-reactive protein; EF, ejection fraction; Tg, triglyceride.
* Model 1: EF, triglyceride, glucose, CRP.
** Model 2: EF, tg-glucose index, CRP.

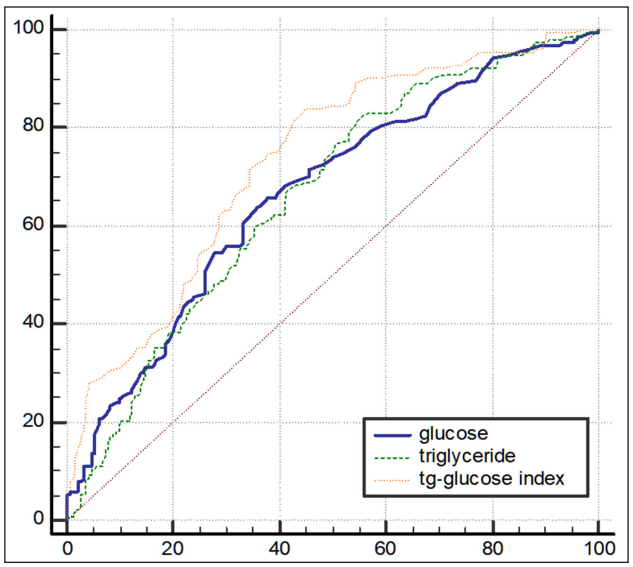

Figure 1. *ROC curve analysis of glucose, triglyceride and tg-glucose index.*

Pairwise comparison of ROC curve analysis showed that the predictive power of tg-glucose index of SVGD was better than serum triglyceride and glucose levels (tg-glucose index and glucose: difference between area under curve [AUC]: 0.0650, SE: 0.0310, z statistics 2.097 and p=0.0360; tg-glucose index and triglyceride: difference between AUC: 0.0700, SE: 0.0237, z statistics: 2.954 and p=0.0031; triglyceride and glucose: difference between AUC: 0.00492, SE: 0.0426, z statistics 0.115 and p=0.9081) (Fig. 1).

Discussion

The most important results of this study are; 1) Insulin resistance is associated with coronary artery disease, and this relationship is also valid for SVGD, 2) The risk of stenosis in SVGs of patients with low ejection fraction is higher than those with normal EF, 3) Serum triglyceride and glucose values and tg-glucose index, which is a biomarker calculated using serum triglyceride and glucose levels and gives information about insulin resistance, was found to be higher than control patients, 4) Tg-glucose index was better than serum glucose and triglyceride levels in predicting SVGD in ROC curve analysis, 5) Tg-glucose index which can be calculated using routine biochemistry studies, is associated with SVGD and is a biomarker that can be used to determine the SVGD in daily practice.

Insulin resistance is a condition that may result in type 2 DM, coronary artery disease, polycystic ovary syndrome, metabolic syndrome, and obesity-related malignancy[16]. Insulin resistance, which is assumed to be chronic inflammation in pathogenesis, leads to the formation of a vicious circle as it leads to an increase in the inflammatory process. Its relationship with coronary artery disease can be explained by the fact that increased serum glucose and insulin levels trigger oxidative stress and cause dyslipidemia due to its effect on lipid metabolism[17]. Nitric oxide (NO), which is known to be an important vasodilator and anti-oxidative molecule, stimulates glucose transport in muscle and adipose tissue and increases glucose oxidation while reducing hepatic glycogen synthesis. In insulin resistance state, the NO synthesis stimulated by insulin is selectively impaired[18]. In patients with a high Tg-glucose index, arterial stiffness was also detected higher and this indicates that the level of nitric oxide in this group may be lower[19]. In addition, the level of ntric oxide is inversely related to the severity of the disease in patients with acute coronary syndromeand the fact that it was found to be even lower in those who underwent coronary bypass compared to those who underwent percutaneous intervention; suggests that the triglyceride glucose index may be higher in these patients[20]. SVGD develops on the basis of thrombosis or intimal hyperplasia in the early postoperative period and atherosclerosis in the period after 1 year. Therefore, it is possible to think that risk factors of atherosclerosis such as DM, HT, smoking and age are also valid for SVGD.

Within 10 years after coronary artery bypass operation using SVG, up to 20% of patients need revascularization[21]. Lesions and restenosis evaluated as noncritical in coronary angiography cause chronic angina in most of the patients. Although DM, which is a major risk factor for atherosclerosis, has been identified as an independent risk factor for SVGD in some studies, there are also studies suggesting that this theory is not valid[22,23]. In our study, patients in the group with and without SVGD were found to be similar in terms of the frequency of DM. The thesis that high blood glucose level is inversely related to SVG patency, whether DM is diagnosed or not, was also demonstrated in our study.

Kubiak et al. found that patients with SVG stenosis had a lower ejection fraction in the study in which optical coherence tomography was used[24]. Our study also supports these results.

The relationship between high serum LDL and low HDL and SVGD has been emphasized in studies[25,26].

The results of our study do not support these data. In obtaining these results; it should be kept in mind that the LDL levels of the patients in both groups were above the targeted value and that the rate of statin use was 63%. The result that the frequency of SVGD is higher in patients with high triglycerides compared to the control group was also shown in our study.

Tg-glucose index is a biomarker that can be calculated from routine biochemistry tests and can provide indirect information about insulin resistance. The fact that the insulin level can be calculated according to the HOMA-IR value without the need increases the usability rate of this index. The relationship of high tg-glucose index with the presence, severity and prognosis of coronary artery disease has been demonstrated in many studies. Mao et al. conducted a study of 791 non-ST elevation acute coronary syndrome patients and followed all patients for 12 months and showed that high tg-glucose index was a risk factor for the development of major cardiovascular events[27]. Another study in which 2840 patients evaluated with coronary computed tomographic angiography were included. In the study, it was found that the tg-glucose index was associated with coronary artery disease[28].

Our study also shows that the tg-glucose index is significantly higher in patients with SVGD compared to controls and is better in predicting the disease than glucose and triglyceride levels.

This study has multiple limitations such as being single centered and retrospective. The HOMA-IR level could not be calculated because the insulin level was not routinely studied in the patients, and the tg-glucose index and the HOMA-IR level could not be compared. The data in our study should be supported by prospective, multicenter and studies including comparative results.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Hepatoprotective Effects of Sinapic Acid in the Streptozotocin-Induced Diabetic Rats

Streptozotosin ile İndüklenen Diyabetik Sıçanlarda Sinapik Asidin Hepatoprotektif Etkileri

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ABSTRACT

Aim: *Hepatotoxicity is one of the most important secondary complications of diabetes. The leading causes of diabetes-induced liver damage are oxidative stress and inflammation. Sinapic acid (SA) has been proposed as a potent antioxidant and antiinflamatuar. In the present study, we aimed to investigate the hepatoprotective effects of SA by evaluating TNF-α, AST, ALT levels, and histological changes in the experimental diabetes model.*

Material and Method: *Rats were divided into four groups (n=7): Sham (S), SA, Diabetic (D), Diabetic+Sinapic Acid (D+SA). S group was given only saline by intragastric (i.g.). SA group was received 20 mg/kg/day SA by i.g. for 28 days. D group was injected with a single dose of 50 mg/kg streptozotocin (STZ) intraperitoneal (i.p.). D+SA was injected with a single dose of 50 mg/kg STZ i.p. and received 20 mg/kg/day SA by i.g. for 28 days. Tumor necrosis factor-alpha (TNF-α) expression was measured using the immunohistochemical method to assess inflammation in the liver. The liver was stained with Masson's trichrome (MT) stain to evaluate possible fibrosis in the liver and hematoxylin-eosin (H-E) stain for histological examination. In addition, serum aspartate aminotransferase (AST) and alanine transaminase (ALT) levels, which is liver function tests, were measured.*

Results: *S and SA groups had normal histological architecture and negative TNF-α immunoexpression. The D group had higher AST and ALT levels and MT staining intensity than the S group. In addition to severe TNF-α immunoexpression, histopathological changes such as vascular dilatation, apoptotic cells, and infiltration of inflammatory cells were observed in group D. TNF-α immunoexpression histopathological changes, AST and ALT levels decreased in the D+SA group compared to the D group.*

Conclusion: *Our study revealed that SA might have a hepatoprotective effect against hepatotoxicity in STZ-induced diabetic rats.*

Key words: *diabetes; liver; rat; sinapic acid; TNF-α*

ÖZET

Amaç: *Hepatotoksisite diyabetin en önemli sekonder komplikasyonlarından biridir. Diyabetin neden olduğu karaciğer hasarının ana nedenleri oksidatif stres ve inflamasyondur. Sinapik asidin güçlü bir antioksidan ve antiinflamatuar olduğu öne sürülmüştür. Bu çalışmada, deneysel diyabet modelinde sinapik asidin (SA) hepatoprotektif etkilerini TNF-α, AST, ALT seviyeleri, MT boyama yoğunluğu ve histolojik değişiklikleri değerlendirerek araştırmayı amaçladık.*

Materyal ve Metot: *Sıçanlar dört gruba ayrıldı (n=7): Sham (S), SA, Diyabetik (D), Diyabetik+Sinapik Asit (D+SA). S grubuna intragastrik (i.g.) yolla serum fizyolojik verildi. SA grubuna 28 gün boyunca i.g. yolla 20 mg/kg/gün SA verildi. D grubuna tek doz 50 mg/kg STZ intraperitoneal (i.p.) enjekte edildi. D+SA grubuna, tek doz 50 mg/kg STZ i.p. yolla enjekte edildi ve 28 gün boyunca 20 mg/kg/gün SA i.g. yolla verildi. Tümor nekroz faktör-alfa (TNF-α) ekspresyonu immünohistokimyasal yöntemle değerlendirildi. Karaciğerde olası fibrozisi değerlendirmek için Masson's trichrome (MT) boyası ve histolojik inceleme için hematoksilen-eozin (H-E) boyası ile karaciğer boyandı. Ayrıca karaciğer fonksiyon testleri olan serum AST ve ALT seviyeleri ölçüldü.*

Bulgular: *S ve SA grupları normal histolojik mimariye ve negatif TNF-a immüno-ekspresyonuna sahipti. S grubu ile karşılaştırıldığında, D grubu daha yüksek AST ve ALT seviyelerine ve MT boyama yoğunluğuna sahipti. D grubunda şiddetli TNF-α immün ekpresyonunun yanı sıra vasküler dilatasyon, apoptotik hücreler ve inflamatuar hücrelerin infiltrasyonu gibi histopatolojik değişiklikler gözlendi. D grubu ile karşılaştırıldığında D+SA grubunda TNF-α immunoexpression, histopatolojik değişiklikler, AST ve ALT seviyeleri azaldı.*

Sonuç: *Çalışmamız, STZ ile indüklenen diyabetik sıçanlarda SA'nın hepatotoksisiteye karşı hepatoprotektif bir etkiye sahip olabileceğini ortaya koydu.*

Anahtar kelimeler: *diyabet; karaciğer; sıçan; sinapik asit; TNF-α*

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Introduction

The liver is one vital organ in the body, which performs many vital functions such as detoxification, secretion, synthesis, and storage. Liver damage, fibrosis, and liver inflammation have occurred due to many pathologies such as diabetes and viral infections[1]. Concern regarding diabetes is that diabetes can cause severe symptoms that can affect multiple vital organ systems such as hepatotoxicity, nephrotoxicity, retinotoxicity, neurotoxicity and are difficult to reverse[2]. Diabetes is thought to be one of the most important causes of liver disease. Therefore, the prevalence of liver disease in diabetic patients is quite high[3]. Two critical parameters of diabetes-induced liver injury are inflammation and oxidative stress[4]. Increased inflammatory response and oxidative stress are caused by hepatocyte injury and its death[2]. Proinflammatory cytokines such as TNF-α play an essential role in the pathogenesis of diabetes[5]. Hyperglycemia active the release of pro-inflammatory cytokine TNF-α that is produced mainly in macrophages[6].

Primary prevention and early treatment are necessary to avoid late diagnosis and advanced damage of diabetes. The growth and development of diabetic complications cause acute metabolic diseases such as obesity, insulin resistance, hyperglycemia, and hyperlipidemia[7]. Previous studies have reported that diabetes is associated with liver pathologies such as fibrosis, cirrhosis, increased liver function enzymes, and abnormal glycogen and fat accumulation in the liver[1,8].

Since antidiabetic drugs cause undesirable side effects, it has been observed that the patient develops resistance after prolonged using[9]. New treatment strategies are needed due to the limited effectiveness of existing treatments caused by these chronic symptoms in the long run. Animal models have long played a critical role in the study and elucidation of disease pathophysiology, identifying target therapeutic molecules, and evaluating new therapeutic agents and treatments *in vivo*/*in vitro*. SA, found in various plants, has been reported to be an antihyperglycemic, antiinflamatuar, and antioxidant agent[10–12]. However, the mechanism of action of SA on the liver in diabetic animals is not fully understood. Therefore, we aimed to assess the possible protective effects of SA in the hepatotoxicity caused by STZ in diabetic rats by determining TNF-α expression, liver function tests, and structural changes in the liver.

Materials and Methods

Drugs and Chemicals

SA (Sigma CAS number: 530-59-6) was acquired from Sigma-Aldrich. STZ (sc-200719) and TNF-α primary antibody (sc-52746) was obtained from Santa Cruz Biotechnology (Dallas, TX, United States).

Experimental Animals and Design

The experiment protocol was approved by Van Yüzüncü Yil University Animal Experiments Local Ethics Committee (approval number: 2019/12), Van, Turkey. In our study, we used a total of 28 adult *Wistar albino* rats (200–250 g weighing and 2–3 months old) obtained from Van Yüzüncü Yil University Experimental Medicine Application and Research Center. The animals were allowed to live under standard conditions (24±2°C, 12 h light/dark cycle), and their water and foods were given as ad libitum. The animals were grouped into 7 in each group.

1. S group: The sham group was received saline for 28 days.
2. D group: All animals were injected 50 mg/kg with a single dose of STZ (i.p.)[12,13].
3. SA group: All animals in this group were administered 20 mg/kg with a dose of SA for 28 days (i.g.)[14].
4. D + SA group: All animals in this group were administered 20 mg/kg with a dose of SA (i.g.) after being administered STZ for 28 days.

Collection of Samples

The thoracic region was dissected, and blood taken from the heart was kept in heparinized tubes. The blood taken from the heart's left ventricle from the dissected thoracic region was transferred to heparinized tubes. For histological and immunohistochemical examination, liver tissue from rats was immersed in formalin solution for fixation.

Measurements of Liver Function Markers

Serums were obtained by centrifuging the blood samples at 3000 rpm (10 min). Then, serum was collected to measure AST and ALT levels. The samples were analyzed to determine ALT and AST levels via an automated biochemical autoanalyzer (Abbott, Architect ci16200, USA).

Histological Analysis

After fixation and routine tissue processing, the liver was embedded in paraffin. Liver sections taken from paraffin blocks with a thickness of 5 μm were stained with H-E for histopathological evaluation of the liver and stained with M-T staining for possible liver fibrosis evaluation. Sections were examined by light microscopy (Olympus BX53, Japan). Stained sections were examined, an average of 10–15 areas were evaluated by random sampling for the liver of each animal in the groups. The findings were evaluated semi-quantitatively according to the degree of damage observed in the examined regions. Accordingly, it was evaluated as: normal tissue: –, very minor damage: + (damage <25%), minor damage: ++ (25–50%), medium damage: +++ (50–75%), severe damage: ++++ (damage >75%).

Immunohistochemical Analysis

The streptavidin peroxidase method was used for immunohistochemical analysis. 5 μm thick sections taken from paraffin blocks of the liver were deparaffinized and rehydrated and then incubated in 3% Hydrogen peroxide (H_2O_2), citrate buffer (ph 6.1), Ultra V Block, TNFα antibody (Santa Cruz Biotechnology, dilution ratio: 1/100), Biotinylated Goat Anti-Polyvalent and Streptavidin–peroxidase conjugate, respectively. Sections were washed in distilled water and then incubated in Diaminobenzidine (DAB) as a chromogen and stained with Mayer's hematoxylin as a counterstain. Immune positive cells in the sections were counted and evaluated by H-score.

Statistical Analysis

Statistical analyses were performed by using SPSS 21.0 software. The one-way analysis of variance (ANOVA) was used to determine the differences between the groups, followed by Tukey post hoc. P≤0.05. All group data were expressed as mean ± standard deviations (SD).

Results

Effects of SA on levels of AST and ALT in diabetic rats

We assessed liver function markers and found significant increases in AST and ALT levels in the D group compared to the S group (p<0.05). But AST and ALT significantly decreased in the D+SA group compared to the D group (p<0.05). There was no significant difference in the SA group compared to the control group (Table 1).

Histological Observations of Liver Tissues With H-E and MT Stainings

In histological examination with H-E stain, S (Figure 1A) and SA (Figure 1D) groups had normal histological structure. Vascular dilatation, apoptotic cells, and infiltration of inflammatory cells were seen in the D group (Figure 1B). However, there were fewer apoptotic cells and infiltration in the D+SA group compared to the D group (Figure 1C).

In the light microscopic examination of the MT staining performed to evaluate fibrosis in the liver, dense fibrous tissue was found mainly around the vessel in group D (Figure 2B) compared to group S (Figure 2A). However, SA treatment reduced fibrosis in diabetic rats (Figure 2C). MT staining of the SA group was similar to the S group.

Immunohistochemical Evaluation of TNF-α in the Liver

To determine the effects of SA on inflammation in the hepatic tissue, we assessed the expressions of the TNF-α using the immunohistochemical method. S (Figure 3A) and SA (Figure 3D) groups were negative. It was found that the expressions of TNF-α increased in the D group and especially around the central vein (Figure 3B). But, SA treatment reduced TNF-α expression in the liver tissue of STZ-induced diabetic rats (Figure 3C). The TNF-α score is given in Figure 4.

Table 1. *Effects of the treatments of SA on AST and ALT levels in diabetic rats*

	Groups			
Parameters	C	D	D + SA	SA
AST activity (mIU/L)	145,00±16,06 [a]	459,71±91,72 [b]	245,71±32,08 [a,b]	117,57±5,99 [a]
ALT activity (IU/L)	48,57±4,38 [a]	319,00±52,44 [b]	184,57±15,15 [a,b]	40,71±0,94 [a]

Values are expressed as means ± SD.
Significant differences as compared with the D group at P < 0.05.
b Significant differences as compared with the C group at P < 0.05.

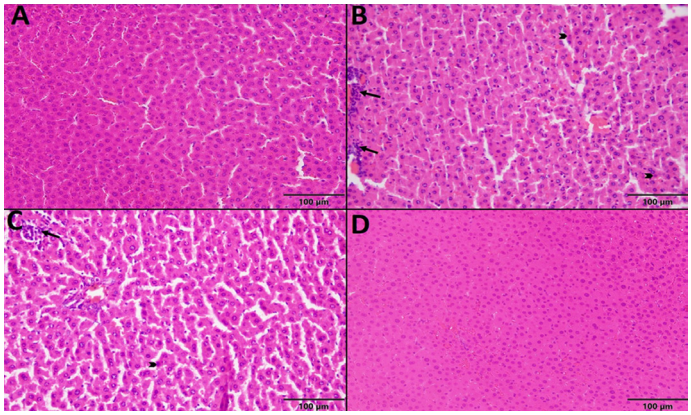

Figure 1. *Light microscopic images of liver sections stained with H-E staining (×40). The vessels were dilated in the D group* ***(B)*** *relative to the S group* ***(A)****, and D+SA treated groups* ***(C)****. Cell infiltration (arrow) and apoptotic cells (arrow head) are observed in group D. Less cell infiltration, and apoptotic cells are kept in the D+SA group compared to the D group (×40).*

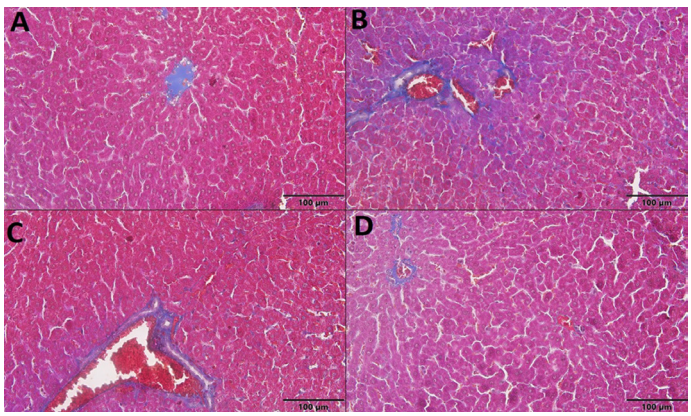

Figure 2. *Light microscopic images of liver sections stained with MT staining (×40). A, sham group; B, D group; C, D+SA group; D, SA group. Collagen fibers are stained with blue. Group D has intense MT staining* ***(B)****. D+SA has moderate MT* ***(C)****.*

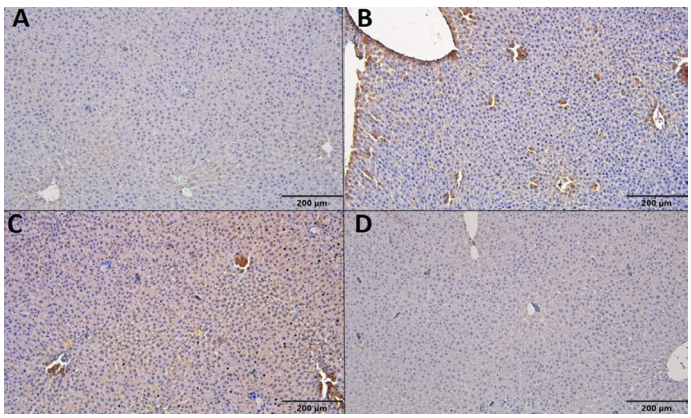

Figure 3. *Representative photomicrographs of immunohistochemical detection of TNF-α in the rat liver tissue (×20). The liver sections of the S* ***(A)*** *and SA* ***(D)*** *groups are negative. The intense immunoexpression of TNF-α in D group* ***(B)*** *and low immunoexpression of TNF-α in D+SA group* ***(C)*** *are present.*

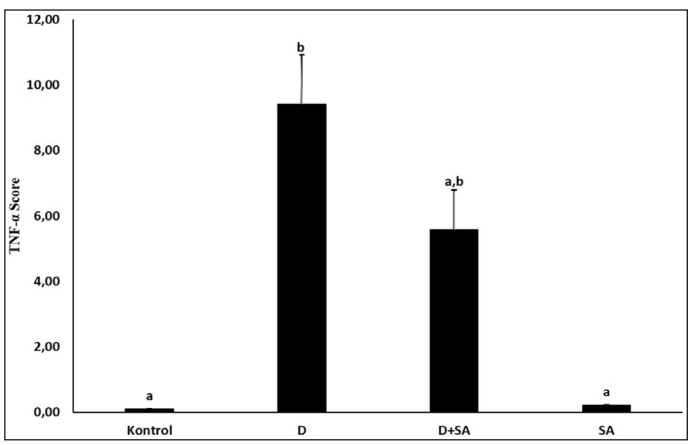

Figure 4. *The immunohistochemical score of TNF-α expression. Intense TNF-α expression in group D and moderate TNF-α expression in group D+SA are observed.*

Discussion

Diabetes, characterized by hyperglycemia, occurs mainly due to impaired insulin synthesis and secretion[15]. It has many harmful effects on the structure and function of many organs, especially the liver. Some antioxidants, including SA, naturally occur as protective and hypoglycemic agents[16]. This study aimed to investigate the possible hepatoprotective effects of SA against SZT-induced hepatotoxicity.

It has been reported that AST and ALT increased in STZ-induced diabetic animals. The increase in levels of these enzymes is an indication of disruption of hepatocyte membrane integrity[17]. Therefore, these enzymes are routinely used as serum enzyme markers in detecting liver diseases[18]. In our study, AST and ALT levels increased in the untreated diabetic group. But, SA treatment decreased AST and ALT levels in the D+SA group. Consistent with our study, Yang and Kang revealed that serum AST and ALT levels increased in STZ-induced diabetic rats. Still, quercetin and resveratrol treatment decreased the increased AST and ALT levels[19]. Elevated AST and ALT levels in serum are indicators of abnormal liver function resulting from their release into the bloodstream from liver-damaged cells. The present study reveals that SA can exert a hepatoprotective effect against STZ-induced hepatotoxicity by reducing the level of liver function enzymes. Our findings are compatible with the literature[20].

Histopathological examinations with light microscopy are used in pathophysiology to give the morphological structures of cells that can change when exposed to oxidative stress. Many studies have been found in the literature on hepatocyte replacement caused by metabolic diseases and therapeutic treatments[21–24]. In our study, changes such as apoptotic cells, enlargement of central vein, and sinusoids were observed in the light microscopic examination of the liver. But, SA treatment restored these pathological changes in liver histology. Consistent with the histopathological findings of our study, Ghara et al. reported that the liver of diabetic animals exhibits pathological changes such as an abnormal sinusoid and necrosis. Still, Capparis *decidua* extract reduced these pathological changes[25]. Similarly, Nambirajan et al. reported that the liver exhibited changes such as lipid accumulation, necrosis, and swelling of hepatocytes in diabetic rats treated with STZ. Still, the bud and flower of Avaram reduced these pathologies[4].

Hepatocytes play an essential role in the metabolism of different nutrients, especially carbohydrates[26]. The lipid metabolism pathogenesis and high-level glucose play an important role in liver pathogenesis, including liver fibrosis[27]. It has been reported that TGF-β, which is accepted as an indicator of liver fibrosis, increases the expression of extracellular matrix genes and thus causes liver fibrosis by increasing the accumulation of type collagen fibrils[1]. In addition, MT staining was carried out to establish the fibrosis degree or accumulation of collagen. The STZ-induced rat liver tissue sections showed noticeable collagen accumulation. But, SA treatment showed a noteworthy reduction in fibrosis in STZ-induced rats. These findings revealed that SA plays a significant role in liver protection, as evident by low collagen accumulation in the SA treatment group. Our histopathological findings showed that SA reduced liver damage and dysfunction in diabetic rats.

The liver expresses receptors for many stimuli that stimulate inflammatory markers such as TNF-α, which cause the activation of kupffer cells[28]. Inflammation is a pathological condition primarily associated with liver injury induced by diabetic complications[29]. Previous studies have reported the occurrence of liver inflammation in an experimental animal model of STZ-induced diabetes[1]. Wang et al. demonstrated that liver inflammation increased in diabetic rats, but Quercetin and Allopurinol reduced the increased liver inflammation[30]. Similarly, Chang et al. reported that liver inflammation increased in STZ-induced diabetic rats, and Resveratrol decreased the increased liver inflammation[31]. Consistent with the previous study[1,30], according to the immunohistochemical findings of our study, the expression of TNF-α, a marker of inflammation, increased in the liver of diabetic rats. In addition, histopathological findings revealed an increase in the infiltration of inflammatory cells in the liver sections of rats in the diabetic group. However, SA treatment decreased both TNF-α expression and cell infiltration in the liver. These findings of our study reveal that SA may have an anti-inflammatory effect in the liver of diabetic rats.

Conclusion

As a result, the findings of our study demonstrated that SA could have a hepatoprotective effect by reducing the increased inflammation, fibrosis and apoptotic cell

number in diabetic rats induced by STZ. Therefore, although additional studies are needed to support our study's findings, it is suggested that SA can be used as a hepatoprotective agent in diabetic patients.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Time to Reach Primary Percutaneous Coronary Intervention in Patients with ST-Segment Elevation Myocardial Infarction Presenting to the Emergency Department

Acil Servise Başvuran ST Segment Elevasyonlu Miyokart İnfaktüslü Hastaların Primer Perkütan Koroner Girişime Ulaşma Sürelerinin Değerlendirilmesi

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ABSTRACT

Aim: *There are strong recommendations regarding the duration of the primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) patients admitted to the emergency department (ED). Determining these periods in local sources is important in comparing their compliance with current diagnosis and treatment guidelines and their effects on morbidity-mortality.*

Material and Method: *Patients with STEMI who applied to the ED of a tertiary education and research hospital between 01.10.2017 and 01.10.2019, accompanied by the prehospital health system or outpatient, were included in this single-center retrospective study. The time to reach PCI and the effects on mortality and morbidity were evaluated in patients diagnosed with STEMI in the ED or referred from an external center with the diagnosis of STEMI.*

Results: *233 patients were included in the study. The mean age of the patients in the study was 61.84±11.70, and 19.31% were female. The time to reach PCI was 55.55±45.08 minutes in patients admitted directly to our hospital by ambulance, 68.27±57.15 minutes in outpatients, and 30.54±27.39 minutes in patients referred from another hospital, which was significantly different (p<0.001). There was no significant difference between patients with and without complications in terms of arrival time to PCI (medians were 37 vs 42, p=0.054). There was no significant difference between the cases with a mortal course and the cases without mortality in terms of the time of arrival to PCI (medians were 37 vs 43, p=0.914).*

Conclusion: *Although the times seem to be compatible with current guidelines, the situations that increase the average need to be revealed. In particular, it is necessary to take measures to limit the time to reach PCI for outpatients. In this study, although the time to reach PCI complies with current guidelines, it shows that other regulations are needed to reduce STEMI-related mortality.*

Key words: *ST-segment elevation myocardial infarction; primary percutaneous coronary intervention; emergency department*

ÖZET

Amaç: *Acil servise başvuran ST segment yükselmeli miyokart infarktüsü (STEMI) hastalarında primer perkütan koroner girişim (PCI) süresi konusunda güçlü öneriler mevcuttur. Bu sürelerin yerel kaynaklardaki tayini, güncel tanı ve tedavi rehberlerine uygunluğunun ve morbidite-mortalite üzerine etkilerinin karşılaştırılması açısından önemlidir.*

Materyal ve Metot: *Bu tek merkezli retrospektif çalışmaya 3. basamak eğitim araştırma hastanesi acil servisine 01.10.2017 ile 01.10.2019 tarihleri arasında hastane öncesi sağlık sistemi eşliğinde ya da ayaktan başvuran STEMI'lü hastalar dahil edildi. Acil serviste STEMI tanısı konulan veya dış merkezden STMI tanısı alarak sevk ile gelen hastalar hastaların PCI'a ulaşma süreleri ve bu sürelerin mortalite ve morbiditeye etkileri değerlendirildi.*

Bulgular: *Çalışmaya 233 hasta dahil edildi. Araştırmadaki hastaların yaş ortalaması 61,84±11,70 ve %19,31'i kadındı. Ambulansla direkt hastanemize başvuran hastalarda PCI'e ulaşma süresi 55,55±45,08 dakika, ayaktan direkt başvuran hastalarda 68,27±57,15 dakika ve başka hastaneden sevk edilen hastalarda 30,54±27,39 dakika olup anlamlı olarak farklıydı (p<0,001). PCI'ya varış süresi açısından komplikasyon gelişen ve komplikasyon gelişmeyen hastalar arasında anlamlı bir fark yoktu (sırasıyla median 37 ve 42, p=0,054). Mortal seyreden vakalar ile mortalite gelişmeyen vakalar arasında PCI'ye varış zamanı açısından anlamlı bir fark bulunmadı (sırasıyla median 37 ve 43, p=0,914).*

Sonuç: *Her ne kadar süreler güncel klavuzlarla uyumlu görülmekte ise de, ortalamayı yükselten durumların açığa çıkarılması gerekmektedir. Özellikle ayaktan başvuran hastaların PCI'ya ulaşma sürelerini kısıtlayıcı önlemler alınması gerekmektedir. Bu çalışmada PCI'a ulaşma süreleri güncel klavuzlara uygunluk gösterse de STEMI'e bağlı mortaliteyi azaltmak açısından başka düzenlemelere ihtiyaç olduğunu göstermektedir.*

Anahtar kelimeler: *ST segment yükselmeli miyokart infarktüsü; primer perkütan koroner girişim; acil servis*

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Introduction

Acute coronary syndrome (ACS) refers to acute chest pain resulting from impaired myocardial blood flow or other symptoms of myocardial ischemia and electrocardiographic changes that usually accompany clinical presentations due to myocardial ischemia. ACS is a series of events associated with thrombotic coronary artery disease, including non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death[1].

One-third of deaths associated with myocardial infarction (MI) occur within the first few hours after the onset of symptoms[2]. Early application of the treatment, especially reperfusion therapy, in STEMI reduces mortality and morbidity. Reducing treatment delays increases survival, while delayed treatment results in irreversible myocardial damage and death[3].

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion method in patients with STEMI. The American Heart Association (AHA) 2013 STEMI guidelines recommend that primary PCI be completed within 90 minutes for STEMI patients presenting to a hospital that can perform PCI[4].2017 European Society of Cardiology (ESC), in the STEMI Guidelines, the maximum time for electrocardiography (ECG) recording and diagnosis with first medical contact is 10 minutes, the time for PCI is 60 minutes if the patient applied to the center where the primary intervention was performed, and it was stated that it should not exceed a maximum of 120 minutes for patients who applied to the emergency department (ED) with the prehospital health system[5]. In the same guideline, the term 'time from diagnosis to PCI (wire crossing)' is used instead of the term 'door-to-balloon time' (D2B)[5]. In this study, we aim to determine the time to reach primary PCI in STEMI patients admitted to the ED, evaluate the compliance of this time with current diagnosis and treatment guidelines, and compare the effects of this time on morbidity and mortality.

Material and Methods

Our retrospective study is conducted with patients diagnosed with STEMI between 01.10.2017 and 01.10.2019 in the ED of a 3rd level education and research hospital, which 400.000 patients apply annually. This study was conducted with the approval of the local ethics committee numbered 2019/123.

Our study was conducted on patients over the age of 18. Patients brought to our study with the pre-hospital health system, outpatients, and referred from external centers were included. Patients with STEMI detected in the 12-lead ECG (presence of newly developed or newly developing left bundle branch block with ST-segment elevation of 0.20 mV in males, 0.15 mV in females or 0.1 mV and above in other leads in at least two adjacent leads V2 and V3 and posterior myocardial infarction) made up the study population. Patients diagnosed with STEMI in the ED and STEMI patients diagnosed with STEMI in an external center and admitted to our hospital by ambulance were retrospectively scanned using hospital records. Patients admitted to the ED are welcomed by the ED senior assistant and emergency medicine specialist. The first ECG took, patient complaints, the patient's history, and physical examination findings are recorded in the patient's file by the senior assistant. If deemed necessary, consultations of the patients to the relevant departments are made by the senior assistant and emergency medicine specialist through the hospital's electronic information system. In this study, the demographic characteristics of the patients, how long they were admitted to the hospital after admission, how long it took the patients to reach PCI, which coronary artery was treated in PCI were investigated using patient files and hospital records. Admission hours to our hospital and time to reach PCI were determined for patients referred from another hospital where PCI could not be performed. The time taken for admission and referral to the previous hospital was not included in the study. The time between admission to the hospital and admission to PCI was evaluated as the "Arrival to PCI" time. Mortality and morbidity of the patients included in the study within one month after PCI was evaluated by examining hospital records. The relationship between the patients' admission time to the ED and the time to reach PCI and the development of morbidity and mortality were investigated.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (1st quartile – third quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the analysis

of variances (ANOVA). Non-normally distributed variables were analyzed with the Mann Whitney U test or Kruskal Wallis test depending on the count of groups. Categorical variables were analyzed with the chi-square tests. Pairwise comparisons were performed with the Bonferroni correction method. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Multiple logistic regression analyses (conditional forward method) were performed to determine risk factors of mortality. $p<0.05$ values accepted as statistically significant results.

Results

Our study included 233 patients (188 males and 45 females); the mean age was 61.84±11.70 (range 33–93). Median arrival to PCI time was 41 minutes. Arrival to PCI time was one hour or below in the 165 (70.82%) patients while above 2 hours in the 17 (7.30%) patients (Table 1). The number of patients whose first medical contact was our hospital was 163. Median arrival to PCI time for these patients was 52 (range 7 – 420) minutes (Table 2). Arrival to PCI time was 55.55±45.08 minutes in patients who first medical contact to our hospital by ambulance, 68.27±57.15 minutes in patients who visit directly, and 30.54±27.39 minutes in referred patients, significantly different ($p<0.001$) (Table 3).

Fifty (21.46%) patients had known coronary artery disease, 28 (12.02%) patients had a coronary stent, and 6 (2.58%) patients had coronary artery by-pass graft history. Eleven (4.72%) patients were evaluated in the green area, 96 (41.20%) patients were evaluated in the yellow area, 56 (24.03%) patients arrived at the hospital with an ambulance, and 70 (30.04%) patients were referred from another hospital. Ninety-nine (42.49%) patients had anterior MI, 131 (56.22%) patients had inferior MI, and 3 (1.29%) patients had posterior MI. The most common intervention was coronary stent (86.21%). Half (51.93%) of the patients applied to the hospital on weekdays between 00:00 and 15:59. The most common intervention locations were the left anterior descending artery (40.63%) and right coronary artery (45.98%). Seven (3.00%) patients had restenosis, 2 (0.86%) patients had ventricular tachycardia (VT) attacks, 2 (0.86%) patients had atrioventricular (AV) blockage and 2 (0.86%) patients had reintervention. Nineteen (8.15%) cases were mortal; three of them were during the intervention.

Table 1. *Summary of Arrival to PCI time*

Time (minutes)	41 (24 – 64)
≤30	84 (36.05%)
31–60	81 (34.76%)
61–90	34 (14.59%)
.91–120	17 (7.30%)
>120	17 (7.30%)

Data are given as median (1st quartile – 3rd quartile) or frequency (percentage)

Table 2. *Summary Arrival to PCI time, referred patients excluded*

Time (minutes)	52 (30–75)
≤30	41 (25.15%)
31–60	62 (38.04%)
61–90	30 (18.40%)
91–120	13 (7.98%)
>120	17 (10.43%)

Data are given as median (1st quartile – 3rd quartile) or frequency (percentage)

Table 3. *Arrival to PCI time (minute)*

Admission	Mean	Standard deviation	P
Direct visit	68.27	57.15	0.001
Direct by ambulance	55.55	45.08	
Referred	30.54	27.39	

We divided patients into three groups according to Arrival to PCI time (≤30, 31–60, and >60). The percentage of coronary artery disease was significantly higher in the ≤30 groups than in the 31–60 group ($p=0.027$) (Table 4). Admission to green area and yellow area percentages were significantly lower in the ≤30 groups than in the other groups, while referred from another hospital percentage was significantly higher in the ≤30 groups than in the other groups ($p<0.001$) (Table 5). There were no significant differences between groups about age, gender, comorbidities, admission, type of MI, stenosis locations, intervention, time of admission, intervention location, length of stay in the intensive care unit, length of stay in hospital, complications, and mortality (Table 4–6).

There was no significant difference between patients with and without complications concerning Arrival to PCI time (medians were 37 vs 42, $p=0.054$). There was no significant difference between mortal and non-mortal cases concerning Arrival to PCI time (medians were 37 vs. 43, $p=0.914$). We found no significant

Table 4. *Summary of patients demographics and history with regard to groups*

	Arrival to PCI time (minutes)				
	≤30 (n=84)	31–60 (n=81)	>60 (n=68)	Total (n=233)	p
Age	61.01±12.67	63.38±10.73	61.01±11.56	61.84±11.70	0.340
Gender					
Male	69 (82.14%)	69 (85.19%)	50 (73.53%)	188 (80.69%)	0.183
Female	15 (17.86%)	12 (14.81%)	18 (26.47%)	45 (19.31%)	
CAD history	26 (30.95%) [a]	12 (14.81%) [b]	12 (17.65%) [a b]	50 (21.46%)	0.027
Coronary stent history	13 (15.48%)	11 (13.58%)	4 (5.88%)	28 (12.02%)	0.169
CABG history	1 (1.19%)	2 (2.47%)	3 (4.41%)	6 (2.58%)	0.458
Hypertension	54 (64.29%)	56 (69.14%)	45 (66.18%)	155 (66.52%)	0.802
Diabetes mellitus	16 (19.05%)	13 (16.05%)	16 (23.53%)	45 (19.31%)	0.513
Hyperlipidemia	24 (28.57%)	26 (32.10%)	22 (32.35%)	72 (30.90%)	0.846
COPD	3 (3.57%)	5 (6.17%)	7 (10.29%)	15 (6.44%)	0.242

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. PCI, percutaneous coronary intervention; CAD, coronary artery disease; CABG, coronary artery by-pass graft; COPD, chronic obstructive pulmonary disease. Same letters denote the lack of statistically significant difference between groups.

Table 5. *Summary of patients procedural characteristics with regard to groups*

	Arrival to PCI time (minutes)				
	≤30 (n=84)	31–60 (n=81)	>60 (n=68)	Total (n=233)	p
Admission					
Direct visit, green area	0 (0.00%) [a]	7 (8.64%) [b]	4 (5.88%) [b]	11 (4.72%)	<0.001
Direct visit, yellow area	21 (25.00%) [a]	38 (46.91%) [b]	37 (54.41%) [b]	96 (41.20%)	
Direct by ambulance	20 (23.81%) [a]	17 (20.99%) a	19 (27.94%) [a]	56 (24.03%)	
Referred	43 (51.19%) [a]	19 (23.46%) [b]	8 (11.76%) [b]	70 (30.04%)	
Type of MI					
Anterior	37 (44.05%)	37 (45.68%)	25 (36.76%)	99 (42.49%)	0.471
Inferior	46 (54.76%)	44 (54.32%)	41 (60.29%)	131 (56.22%)	
Posterior	1 (1.19%)	0 (0.00%)	2 (2.94%)	3 (1.29%)	
Stenosis locations					
Left main	0 (0.00%)	0 (0.00%)	1 (1.47%)	1 (0.43%)	0.296
Left anterior descending	44 (52.38%)	48 (59.26%)	33 (48.53%)	125 (53.65%)	0.407
Circumflex	20 (23.81%)	22 (27.16%)	21 (30.88%)	63 (27.04%)	0.621
Right coronary artery	47 (55.95%)	40 (49.38%)	36 (52.94%)	123 (52.79%)	0.699
Intervention					
PCI	6 (7.23%)	7 (8.64%)	2 (2.94%)	15 (6.47%)	0.652
Balloon	5 (6.02%)	6 (7.41%)	6 (8.82%)	17 (7.33%)	
Stent	72 (86.75%)	68 (83.95%)	60 (88.24%)	200 (86.21%)	
Time of admission					
Weekdays 00:00–07:59	29 (34.52%)	17 (20.99%)	15 (22.06%)	61 (26.18%)	0.502
Weekdays 08:00–15:59	20 (23.81%)	22 (27.16%)	18 (26.47%)	60 (25.75%)	
Weekdays 16:00–23:59	12 (14.29%)	12 (14.81%)	12 (17.65%)	36 (15.45%)	
Weekend 00:00–07:59	8 (9.52%)	11 (13.58%)	12 (17.65%)	31 (13.30%)	
Weekend 08:00–15:59	10 (11.90%)	9 (11.11%)	4 (5.88%)	23 (9.87%)	
Weekend 16:00–23:59	5 (5.95%)	10 (12.35%)	7 (10.29%)	22 (9.44%)	

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. PCI, percutaneous coronary intervention; MI, myocardial infarction. Same letters denote the lack of statistically significant difference between groups.

Table 6. *Summary of intervention with regard to groups*

	Arrival to PCI time (minutes)				
Intervention location	≤30 (n=84)	31–60 (n=81)	>60 (n=68)	Total (n=233)	p
Left main	0 (0.00%)	4 (5.26%)	1 (1.49%)	5 (2.23%)	0.204
Left anterior descending	34 (41.98%)	31 (40.79%)	26 (38.81%)	91 (40.63%)	
Circumflex	6 (7.41%)	8 (10.53%)	11 (16.42%)	25 (11.16%)	
Right coronary artery	41 (50.62%)	33 (43.42%)	29 (43.28%)	103 (45.98%)	
Length of stay in ICU	2 (2–3)	2 (1–2)	2 (1–3)	2 (1–3)	0.393
Length of stay in hospital	3 (2–4)	3 (2–4)	3 (2–3)	3 (2–4)	0.436
Complications	6 (7.14%)	7 (8.64%)	0 (0.00%)	13 (5.58%)	0.054
Restenosis	4 (4.76%)	3 (3.70%)	0 (0.00%)	7 (3.00%)	
VT attacks	2 (2.38%)	0 (0.00%)	0 (0.00%)	2 (0.86%)	
AV blockage	0 (0.00%)	2 (2.47%)	0 (0.00%)	2 (0.86%)	
Reintervention	0 (0.00%)	2 (2.47%)	0 (0.00%)	2 (0.86%)	
Mortality	7 (8.33%)	6 (7.41%)	6 (8.82%)	19 (8.15%)	0.949
Referred excluded mortality	3 (7.32%)	3 (4.84%)	5 (8.33%)	11 (6.75%)	0.733

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. ICU, intensive care unit; VT, ventricular tachycardia; AV, atrioventricular. Same letters denote the lack of statistically significant difference between groups.

Table 7. *Significant risk factors of the mortality, multiple logistic regression analysis*

	β coefficient	Standard Error	p	Exp (β)	95% CI for Exp (β)	
Age	0.084	0.027	0.002	1.087	1.030	1.147
Female gender	1.386	0.651	0.033	3.998	1.116	14.328
Left anterior descending stenosis	1.584	0.653	0.015	4.872	1.355	17.523
Complication	3.940	0.855	<0.001	51.436	9.635	274.601
Constant	-9.936	2.144	<0.001			

Dependent variable: Mortality; Nagelkerke R^2=0.363; Correct prediction=92.70%; CI, confidence interval.

correlation between Arrival to PCI time and age (r=-0.013, p=0.844), Arrival to PCI time, and length of stay in an intensive care unit (r=-0.079, p=0.229), Arrival to PCI time, and length of stay in hospital (r=-0.052, p=0.433).

We performed multiple logistic regression analyses to determine significant risk factors of mortality. We found that the risk of mortality increases with age (p=0.002). Female patients had a 3.998-fold higher risk of death than male patients (OR: 3.998, 95% CI: 1.116–14.328, p=0.033). Patients with left anterior descending artery stenosis had a 4.872-fold higher risk of death than the other patients (OR: 4.872, 95% CI: 1.355–17.523, p=0.015). Patients who had a complication during/after the intervention had a 51.436-fold higher risk of death than the other patients (OR: 51.436, 95% CI: 9.635–274.601, p<0.001). Other variables included in the model, Arrival to PCI time (p=0.219), coronary artery disease history (p=0.497), coronary stent history (p=0.431), coronary artery bypass graft history (p=0.287), admission unit (p=0.975), type of MI (p=0.985) and time of admission (p=0.948) were found to be non-significant (Table 7).

Discussion

Our study once again emphasizes the importance of the time to reach PCI in patients with STEMI.

STEMI account for approximately 25% to 40% of acute myocardial infarction (AMI) cases. Although in-hospital mortality rates of 5–6% and annual mortality rates of 7–18%, and STEMI-related mortality have decreased in recent years, they are still an important cause of mortality[4].

Delays in treatment lead to increased mortality and deterioration of cardiac functions. D2B, the time between hospital arrival and PCI, is strongly associated with survival in STEMI patients. It is recommended that more than 75% of STEMI patients have a D2B time of fewer than 90 minutes[6].

The demographic characteristics of the patients in our study are similar to those of published studies. 19.31% of the patients included in our study were female, and 21.46% had a history of coronary artery disease. Hypertension (66.52%) was the most common comorbidity. Similar to other studies, the left anterior (LAD) and right coronary arteries (40.63%, 45.98%, respectively) were found to be the coronary arteries with the most stenosis[7,8]. The rate of reaching PCI in 30 minutes or less in patients with a history of coronary artery disease was statistically significantly higher than the other patient groups (p=0.027).

The first place of application for 69.95% of the patients included in our study was the ED of our hospital, 45.9% were outpatients, and 24.03% of them came to our ED with the pre-hospital emergency health system (EMS). 85.4% of patients achieved PCI in less than 90 minutes. On the other hand, in 81.59% of the patients whose first referral center is our hospital, the time to reach PCI is less than 90 minutes. The time to reach PCI was found to be 68.27±57.15 minutes for outpatients and 55.55±45.08 minutes for patients presenting with EMS. While 66.07% of the patients who came with EMS, which was the first place of application to our hospital, reached PCI under 60 minutes, 61.68% of the outpatients reached PCI below 60 minutes. There was a significant difference between the patient groups, divided into three according to the time to reach PCI and how they applied. While 55.55% of the patients in the 31–60 group, who had time to reach PCI, applied directly to our ED, 20.99% of this group consisted of patients who came directly to our ED by ambulance. While the rate of reaching PCI at 30 minutes and less in outpatients was significantly lower than the other groups, the rates of reaching PCI in 30 minutes and less in patients referred from another hospital were significantly higher than the other groups (25%, 51.19%, respectively; p: <0.001). The EMS informing the referred patients before they come to our hospital and the catheter laboratory is activated, the short time to reach PCI can be explained. However, our study did not determine how long it took the referred patients to come to our hospital from the first center they applied. In the TURKMI study, Erol MK et al.[9] reported that from arrival to the first hospital to reach the second hospital was 120 minutes In the same study, similar to ours, most of the patients (49.5%) came by themselves, 11.8% by EMS ambulance. It was found that EMS transferred 38.6% from another hospital where PCI could not be performed, and the D2B time was 36 minutes. In another study published in Turkey, the mean D2B time was 98 minutes in patients who applied directly and underwent PCI and 228 minutes in those who were referred[10]. In another study conducted with 43 801 patients, the D2B time was 83 minutes, and 57.9% of the patients had a D2B time of fewer than 90 minutes[7].

Eleven patients who applied to our ED with atypical findings (long-standing pain, weakness, epigastric pain, etc.) were diagnosed with STEMI. None of these patients could reach PCI in less than 30 minutes. In the study of Takuya Nakahashi et al., 40% of AMI patients presenting with atypical symptoms had a D2B time under 90 minutes, while 66.3% of patients presenting with typical symptoms had a D2B time under 90 minutes. Patients presenting with atypical symptoms in AMI patients had a long time to reach PCI and high 30-day mortality[11].

For STEMI patients presenting to a hospital capable of performing PCI in the AHA, it is recommended that the primary PCI procedure be completed within 90 minutes. In our study, the meantime to reach PCI was calculated as 41 minutes for all patients and 52 minutes for patients whose first application was the ED of our hospital. There was no significant difference between patients with and without complications in terms of arrival time to PCI (medians were 37 vs 42, p=0.054). There was no significant difference between the cases with a mortal course and the cases without mortality in terms of the time of arrival to PCI (medians were 37 vs 43, p=0.914). There was no significant relationship between the time to reach PCI and mortality. The mortality rate was calculated as 8.15%, and it was found to be higher than in other studies[10,12]. When patients referred from another hospital are excluded, the mortality rate drops to 6.75%. This may be due to the delay in the diagnosis period of the patients who came with a referral in the center they applied to before coming to our hospital and the long referral duration. Many studies have reported that shortening

the D2B time increases survival[13–15]. In the study of Cannon et al., it was shown that if the D2B duration is longer than 2 hours, there will be a 41–62% increase in in-hospital mortality[16]. However, there are also studies showing that shortening the D2B time does not affect mortality. In a study evaluating the effect of D2B time on mortality, including 96.738 patients with STEMI who underwent primary PCI between 2005 and 2009, D2B time decreased from 83 minutes to 67 minutes over the years. However, in-hospital mortality (5.0% in 2005–2006 and 4.7% in 2008–2009) was unchanged. Although national D2B improved significantly in patients undergoing primary PCI for their STEMI, in-hospital mortality remained virtually unchanged[12].

In our study, it was also found that mortality increased with age (p=0.002). The risk of death in female patients was 3.998 times higher than in male patients (OR: 3.998, 95% CI: 1.116–14.328, p=0.033). Similarly, in a study, in-hospital and 30-day mortality in STEMI patients was higher in women[17,18]. In addition, in our study, the risk of death in patients with left anterior coronary artery stenosis was found to be 4.872 times higher than in other patients, consistent with the literature (OR: 4.872, 95% CI: 1.355–17.523, p=0.015) [4].

In this study, although the time to reach PCI complies with current guidelines, it shows that there is a need for shortening the time to reach PCI and additional strategies to reduce in-hospital mortality.

Limitations

Our study has several limitations that should be considered. First, the time of onset of symptoms was not evaluated in our study. We could not assess the relationship between the time from onset of symptoms to reaching PCI and mortality. In addition, the application times of the patients who came to our hospital with a referral from another hospital where PCI could not be performed and the time elapsed until they came to our hospital were not included in our study. Our study aimed to evaluate the time it takes to reach PCI and its effect on the survival of patients admitted to our hospital and guide our improvement efforts within the hospital. The time of arrival of the patients coming from an external center to our hospital is under the control of the pre-hospital health system, so it will not be affected by our in-hospital improvement efforts.

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DERLEME / *REVIEW*

Biophysical Overview of Covid-19 Infection

Covid-19 Enfeksiyonuna Biyofiziksel Genel Bakış

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a global pandemic by WHO on March 11, 2020. Coronavirus disease (COVID-19) is the infectious disease caused by SARS-CoV-2. It is transmitted from person to person through droplets, progresses asymptomatically in 70% of the sufferers, while it may manifest itself in severe clinical conditions, ranging from viral upper respiratory tract infection to pneumonia, sepsis, septic shock, and even acute respiratory distress syndrome (ARDS), in symptomatic patients. Studies on the epidemiological and clinical features of COVID-19 have shown that these patients can develop symptoms of mild or severe acute respiratory infection. In cases with mild symptoms, upper respiratory tract symptoms such as fever, dry cough, and fatigue may develop, and abnormal chest CT findings may also be present. In cases with severe symptoms, dyspnea, diarrhea, severe pneumonia, ARDS or multiple organ failure develop, and mortality rates vary between 4.3% and 15% according to different study reports.

Key words: *COVID-19; hemorheology; respiratory system; body fluids; oxidative stress; sedantary life*

ÖZET

Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) enfeksiyonu, 11 Mart 2020 tarihinde DSÖ tarafından küresel bir pandemi ilan edilmiştir. Koronavirüs hastalığı (COVID-19), SARS-CoV-2'nin neden olduğu bulaşıcı hastalıktır. Damlacık yoluyla kişiden kişiye bulaşan SARS-CoV-2 enfeksiyonu, hastaların %70'inde asemptomatik olarak görülmektedir. Semptomatik hastalarda ise viral üst solunum yolu enfeksiyonundan pnömoni, sepsis, septik şok ve hatta akut solunum sıkıntısı sendromuna (ARDS) kadar değişen ciddi klinik durumlarla seyredebilmektedir. COVID-19'un epidemiyolojik ve klinik özellikleri üzerine yapılan çalışmalarda, bu hastalarının hafif veya şiddetli akut solunum yolu enfeksiyonu semptomları geliştirebileceğini gösterilmiştir. Hafif semptomları olan olgularda ateş, kuru öksürük, yorgunluk gibi üst solunum yolu semptomları gelişebilir ve anormal göğüs BT bulguları da olabilir. Farklı çalışma raporlarına göre, şiddetli semptomları olan vakalarda nefes darlığı, ishal, şiddetli pnömoni, ARDS veya çoklu organ yetmezliği gelişmekte ve ölüm oranları %4,3 ile %15 arasında değişmektedir.

Anahtar kelimeler: *COVID-19; hemreoloji; solunum sistemi; vücut sıvıları; oksidatif stres; sedanter yaşam*

Introduction

Coronavirus Disease 2019 (COVID-19) is a very contagious viral disease that has spread globally resulting in high morbidity and mortality rates. Comorbidities like pulmonary or cardio-vascular diseases (CVD), diabetes, immune system disorders and older age deteriorate the clinical onset. After being activated by spike protein, the virus binds to human angiotensin-converting enzyme 2 (ACE2) receptor. ACE2, expressed mainly in lungs, also in heart, kidneys, and vascular endothelial tissue, is excessively activated in CVD and has been reported to be one of the responsible causes for the multiple organ failure in COVID-19[1].

Biophysical Effects of COVID-19 on Hemoreologic Parameters

Inflammation status in COVID-19 triggers myocardial injury via increases in serum levels of troponin and also in inflammatory bio-markers like CRP, ferritin, fibrinogen, D-dimer, IL-6, and LDH, all acting preliminarily for the cytokine storm. Fibrinogen, one of the most important determinants of plasma viscosity (PV) with its big molecular structure and asymmetry, increases extensively in plasma of COVID-19 patients. Fibrinogen's pivotal function in coagulation is even to constitute a clot in vessel injuries for stopping the bleeding or to aggrevate thrombosis during inflammatory process. Clinical onset of thrombosis seen in COVID-19 can be followed up via plasma fibrinogen and D-dimer levels, which is a degradated product of cross-linked fibrin[2]. Consequently, blood viscosity (BV) also increases due to elevated levels of

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acute phase reactants and immunoglobulins via inflammatory process. Elevated fibrinogen, PV and BV foster erythrocyte aggregation that ends up in higher erythrocyte sedimentation rate[3].

Another target of COVID-19 is the endothelial tissue, that consitutes the largest tissue in human body. Endothelial dysfuction accompanied with generalized inflammation may lead to pro-coagulative state resulting in micro-vascular and macro-vascular thrombosis in arterial and venous circulation[2,4]. COVID-19 clinical onset have to be evaluated with a multi-disciplinary approach, especially in CVD by means of cardiovascular co-morbidities and hemorheological parameters. More scientific data should be elucidated to determine the mechanisms of cardio-vascular system and its complications in order to minimize morbidity and mortality rates.

Biophysical Effects of COVID-19 on Respiratory System

COVID-19 effects generally respiratory system besides with cardiovascular and immune systems. As the virus enters mostly via nose and conducting airways, respiratory droplets reach to alveoli[5]. Alveolar wall (AW) thickens due to oxidative stress, inflammation, secreted cytokines, endothelial dysfunction and increased permeability resulting in fibrosis of alveolocapillary membrane (ACM). Leakage of serum proteins and formation of fibrin exudates into alveolar space induces alveolar flooding and deteriorates surfactant production from alveolar type II cells[6]. Phospholipid content of pulmonary surfactant is responsible for lowering the surface tension of alveoli during inspiration and for inhibiting alveolar collapse (AC) after expiration[6,7]. Surfactant dysfunction of injured alveoli terminates in increased intraalveolar pressure (AP) and transmural tension according to LaPlace Law. Besides, gas diffusion rate across ACM slows down due to diminished partial pressure of oxygen (PaO_2) and thickened AW as described by Fick's Law[7,8]. Ventilation in lungs occurs because of a pressure gradient between atmospheric pressure and intraalveolar pressure (AP) [9]. Fluid adhesion and negative pressure hold visceral and parietal pleura attached to each other. When parietal movement of thorax cavity pulls the lungs encovered with pleural layers (PL), diaphragm muscle contracts, the lungs expand, thorax volume increases and intrathoracic pressure decreases during inhalation due to Boyle's Law[8,9]. Pleural fluid is a viscous fluid that fills pleural cavity allowing PL to glide over each other. Negative intrapleural pressure is controlled by hydrostatic and oncotic pressures. Pleural layers are thickened probably followed by pleural effusion in severe COVID-19[9,10]. Gas exchange (GE) in central and peripheral body sites gets disturbed resulting in decreased PaO_2 described with Dalton's Law[4,5]. These mentioned pathologic alterations induce AC and impaired GE in a vicious cycle of hypoxia and acute respiratory distress syndrome. Evaluation of respiratory and cardiovascular systems within the basis of gas laws and body fluids should be considered for diagnosis, treatment and follow-up of COVID-19 patients.

Biophysical Effects of COVID-19 on Body Fluids

Transmission of COVID-19 mainly occurs via respiratory droplets firstly targeting both upper and lower respiratory tracts. As COVID-19 virus reaches to terminal bronchi and alveoli, its spike protein binds to alveolar type-2 cells (AT2) by angiotensin converting enzyme-2 receptors. Encountering of viral burden with host cells and cell membranes induces inflammatory signals that are secreted from AT2 recruiting neutrophils and macrophages to infection site[1]. Neutrophil infiltration acts as the first defense mechanism and secrete reactive oxygen species (ROS) to destroy infected cells. Macrophages secrete many cytokines that recruit immune cells to infection site. Activated neutrophils and macrophages, and released cytokines are the chief factors that trigger the inflammatory response in COVID-19 infection via vasodilation, leakage in capillaries and thickening of alveolar membrane[11,12]. Endothelial cells are the other target for COVID-19 virus effected from increased local blood pressure and weakening of cell junctions, resulting in injured basal membrane. Intravascular fluid transfers through these leakage areas leading to interstitial oedema encircling both capillaries and alveoli. Inflammation originated from activated immune system and ROS-induced mechanisms transform the alveolar membrane into a thickened surface. Surfactant secreted from AT2 is diluted because of intra-alveolar fluid and surfactant synthesis is deteriorated due to inflammation and oedema conditions[4,13]. As infection gets more severe, intra-alveolar fluid becomes more infectious rich in protein, which also retracts fluid from intravascular compartment into interstitial space. Vasodilatation, injured basal membrane and cytokine storm trigger endothelial

dysfunction in respiratory capillaries leading to uncontrolled clotting and thrombosis. Thrombosis is not just limited in respiratory system, the whole circulatory system becomes under threat for thrombosis including additional clotting factors and platelets[4,14]. This mentioned issues induce alveolar collapse, increased permeability in capillaries, pulmonary oedema and impaired gas exchange resulting in a vicious cycle of hypo-oxygenation and respiratory distress syndrome[15]. Body fluids, endothelial dysfunction and gas exchange within an aspect of biophysical evaluation should be considered thoroughly in diagnosis, treatment and follow-up of COVID-19 infection.

Biophysical Effects of COVID-19 on Oxidative Stress

COVID-19 is a viral infection caused by a RNA virus disturbing many human body systems, especially the respiratory system[16]. Respiratory viral infections induce lipid and protein peroxidation, cytokine and chemokine production, inflammation and cell death. High burden of reactive oxygen species (ROS) and free radicals (FR) are produced from pathologic processes metabolic reactions in COVID-19 infection[17,18]. Oxidative stress (OS) is described as the imbalance of pro-oxidant and anti-oxidant systems due to increase in pro-oxidants, resulting in ROS production and cell damage[19]. OS status can be tolerated by anti-oxidant defense mechanisms including many enzymes, co-factors, vitamins, minerals and trace elements. These anti-oxidant substances scavange the harmful effects ROS and FR in order to maintain the physiological metabolism of biomolecules like DNA, RNA, proteins, carbohydrates and lipids[20]. If the optimum physiological metabolism cannot be achieved, pro-oxidants would promote a pro-inflammatory environment including biochemical, biophysical, biomolecular and nuclear pathways[18]. This physiopathological scenario is similar by means of COVID-19 infection. The vulnerable point of COVID-19 infection is that little data have been elucidated yet related with this disease. A destructive over-reaction in immune system called as "cytokine storm" stimulates the over-production of inflammation markers closely in relation with ROS and FR. An uncontrolled generalized immune response plays the leading role for COVID-19 infection in many systems of the body, primarily in respiratory system[21]. COVID-19 infected individuals who have comorbidities such as hypertension, diabetes, obesity and cardiocerebrovascular diseases are at more risk for OS[18]. Oxidative stress is accepted as a probable cause associated with clinical onset of COVID-19. Oxidative stress can be reduced by endogenous antioxidant enzymes and molecules like glutathione, and exogenous supplementation of zinc, selenium, and vitamin C, vitamin D, vitamin E.

Effects of COVID-19 on Sedantary Life, Circulatory and Pulmonary Dynamics

COVID-19 presents a life-altering challenge for all population that forces all the individuals to live self-isolated in home-confinement. Biological systems such as cardiovascular, pulmonary and muscular systems are effected from this sedentary life style[5,22]. Muscle contractions in lower extremities during physical exercise pumps the burden of blood in venous system back to the right auricula in the heart. On the other hand, diminished physical activity and physical inactivity may promote the stasis of blood in lower extremities resulting in thrombosis[23]. Muscle loss as a result of physical inactivity has a close relationship with microvascular alterations, lowered aerobic capacity, fat deposits in the body, insulin resistance and inflammation[5,22]. A combination of a diet rich in fatty acids and physical inactivity induces insulin resistance observed in dysfunctions of skeletal muscle tissue[24]. Moreover, apetite changes prone to eating more creates a psychological pathology that would induce over-weight individuals having increased rates of metabolic and cardiovascular risk. Increased habit of smoking and/or alcohol abuse in home-confinement interval may change the individual's and the family's life style and may have effects over entire public[25]. A regularly planned physical exercise was accepted to lower the risk factors such as high body fat, dyslipidemia, atherosclerosis, thromboembolism and stroke[22,23]. All issues mentioned above cause burden of oxidative stress and pro-inflammatory process probably resulting in cardiocerebrovascular diseases. Home-based exercises including streching-relaxation exercises, stepping, self exercises utilizing virtual programs and breathing exercises possibly assisted with wearable technologies would be life-saving for conserving cardiovascular, pulmonary and muscular health during isolation period due to social distancing. Another crucial issue is that individuals should organize their daily lives within a plan covering the regulation of diet and calorie restriction.

Conclusion

The present study is a brief and simple summary for the biophysical effects of COVID-19 on various biological systems. These effects possess a clinical manifestation of the infection and its complications in the metabolism. However, there is an urgent need for the introduction of the whole molecular, cellular dynamics of this trial with its clinical effects on the systems. We consider that in the future, with the availability of such quantitative data, functional the effect of COVID-19 infection on biological systems will be elucidated.

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