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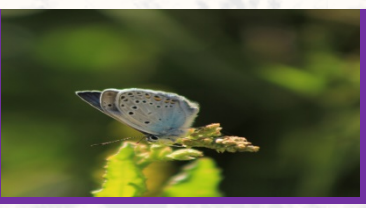

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A comparative study of USG guided fascia iliaca compartment block and femoral nerve block to assist the technique of spinal anaesthesia

Spinal anestezi tekniğine yardımcı olmak amacıyla USG rehberliğinde fasya iliaka kompartman bloğu ve femoral sinir bloğunun karşılaştırmalı çalışması

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Abstract

Background: Proximal femur fractures are very painful, making positioning for regional anaesthesia a challenge. Peripheral nerve blocks are safe and effective for analgesia, and have the advantage of opioid-sparing effects. This study compares the analgesic efficacy of ultrasound-guided fascia iliac compartment block (FICB) and femoral nerve block (FNB) for optimal positioning during spinal anaesthesia for proximal femur fracture surgeries.

Materials and Methods: Ninety patients belonging to ASA I, II, and III, who were posted for surgery on proximal femur fractures, were randomly allocated into two groups of 45 each. Group A patients received USG-guided fascia iliaca block, and Group B patients received USG-guided femoral nerve block. Pain during positioning for spinal anaesthesia was the primary outcome and was assessed using the Numerical Rating Scale (NRS) scores.

Results: Time to onset of block was 4.3 ± 0.9 mins in the FICB group and 2.8 ± 0.6 mins in the FNB group ($p < 0.001$). Time to perform the block was 8.52 ± 2.32 mins in the FICB group and 5.12 ± 1.22 mins in the FNB group ($p < 0.001$). A statistically significant difference was seen between the study groups at 10, 15, and 30 mins after the intervention in terms of NRS pain scores.

Conclusions: We conclude that both the femoral nerve block (FNB) and the fascia iliaca compartment block (FICB) using ultrasound guidance are simple and effective. In our study, patients in Group B had lower NRS scores compared to Group A. The ultrasound-guided FNB may offer faster onset of block and better pain relief than FICB for assisting in positioning for spinal anaesthesia in patients with proximal femur fractures.

Keywords: bupivacaine, femoral nerve block, fascia iliaca compartment block, femur fractures, spinal anaesthesia.

Öz

Amaç: Proksimal femur kırıkları oldukça ağrılıdır ve bu durum spinal anestezi için pozisyon vermeyi zorlaştırır. Periferik sinir blokları, analjezi sağlama açısından güvenli ve etkili yöntemler olup, opioid kullanımını azaltma gibi avantajlara sahiptir. Bu çalışma, proksimal femur kırığı cerrahileri sırasında spinal anestezi öncesi optimal pozisyonlama için ultrason eşliğinde yapılan fascia iliaca kompartman bloğu (FICB) ile femoral sinir bloğunun (FNB) analjezik etkinliğini karşılaştırmaktadır.

Gereç ve Yöntem: ASA I, II ve III sınıfına dahil edilen ve proksimal femur kırığı nedeniyle ameliyat planlanan 90 hasta rastgele iki gruba ayrıldı, her grupta 45 hasta yer aldı. Grup A'daki hastalara ultrason rehberliğinde fascia iliaca bloğu uygulandı; Grup B'deki hastalara ise ultrason rehberliğinde femoral sinir bloğu uygulandı. Spinal anestezi için pozisyonlama sırasındaki ağrı birincil sonuç olarak belirlendi ve Sayısal Ağrı Skalası (NRS) ile değerlendirildi.

Bulgular: Blok başlama süresi FICB grubunda 4,3±0,9 dakika, FNB grubunda ise 2,8±0,6 dakika idi ($p<0,001$). Bloğun uygulanma süresi FICB grubunda 8,52 ± 2,32 dakika, FNB grubunda ise 5,12 ± 1,22 dakika idi ($p<0,001$). Müdahale sonrası 10, 15 ve 30. dakikalarda NRS ağrı skorları açısından gruplar arasında istatistiksel olarak anlamlı fark görüldü. **Sonuç:** Hem femoral sinir bloğu (FNB) hem de fascia iliaca kompartman bloğu (FICB), ultrason rehberliğinde uygulandığında basit ve etkili yöntemlerdir. Çalışmamızda, Grup B'deki (FNB) hastaların NRS ağrı skorları, Grup A'daki (FICB) hastalara kıyasla daha düşüktü. Ultrason eşliğinde uygulanan FNB, proksimal femur kırığı olan hastalarda spinal anestezi öncesi pozisyonlandırma için FICB'ye göre daha hızlı etki başlangıcı ve daha iyi ağrı kontrolü sağlayabilir.

Anahtar Kelimeler: bupivakain, femoral sinir bloğu, fascia iliaca kompartman bloğu, femur kırıkları, spinal anestezi.

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Highlights

- The objective of this study was to compare the analgesic efficacy of ultrasound-guided fascia iliaca compartment block (FICB) vs. femoral nerve block (FNB) for positioning patients with proximal femur fractures during spinal anaesthesia.
- Both blocks are effective, but ultrasound-guided FNB is superior in terms of quicker onset and better analgesia for positioning patients during spinal anaesthesia

Introduction

Spinal and epidural anaesthesia are the most common regional anaesthesia techniques used for traumatic orthopedic lower limb surgeries (1,2). A major hindrance to the performance of central neuraxial blockade in patients with femur fractures is the lack of optimal positioning of patients due to the acute, painful fractures. Minor movements and even slight changes in position cause excruciating pain. Sympathetic activation due to pain leads to tachycardia and hypertension, which can be detrimental in elderly patients who are at high risk of ischemic heart disease (3,4,5). Systemic use of NSAIDs, opioids, and paracetamol for pain relief is often insufficient for optimal positioning for central neuraxial blockade. Peripheral nerve block provides a safe and reliable substitute for systemic analgesia, with an opioid-sparing effect (6,7,8). Ultrasound-guided approaches reduce the local anesthetic (LA) quantity and adverse effects of LA (9,10,11). Regional anaesthesia techniques are considered preferable to minimise the use of systemic opioids. The use of USG-guided peripheral nerve blocks has revolutionised regional anaesthesia. The need for an effective and safe method to assist patient positioning during spinal anaesthesia in patients with painful fractures is of utmost value. The present study was done to compare the efficacy of ultrasound (USG)-guided femoral nerve block (FNB) and fascia iliaca compartment block (FICB) for patient positioning during the performance of the central neuraxial blockade technique. The primary objective was the assessment of pain during positioning for spinal anaesthesia by the Numerical Rating Scale (NRS). Secondary objectives were the assessment of patient satisfaction, quality of patient positioning, adverse effects, and complications.

Material and Methods

During the pre-operative visit, patients were assessed for eligibility for the study and informed about the study interventions and Numerical rating scale (NRS) scores for pain assessment. Written Informed consent for participation in the study was obtained. Patients belonging to ASA class I, II & III, aged between 18 and 80 years, of either gender who were scheduled to undergo elective surgery for proximal femur fractures under spinal anaesthesia were included in the study. Patients with history of allergy to study drugs, infections at site of injection, polytrauma, head injury, morbid obesity and impaired cognition were excluded from the study. Computer-generated random numbers were used to allocate patients into two groups. All patients underwent thorough preoperative evaluation and followed the standard pre-operative fasting guidelines. In the preoperative room, intravenous line was secured and base line vital parameters were recorded with pulse-oximetry, noninvasive blood pressure (NIBP) and electrocardiography (ECG).A linear 7-13 MHz ultrasound-guided probe (Sonosite M-Turbo, USA) was used to view anatomical structures. The block procedures were done by an Anaesthesiologist with an experience of more than five years in USG guided peripheral nerve block techniques. FICB and FNB were carried out in supine position under aseptic conditions. The FICB was given for patients in Group A. Fascia lata and fascia iliaca are located as two hyper-echoic lines with the Ultrasound transducer placed transversely on the thigh below the inguinal ligament at the junction of medial one third and lateral two thirds of the line joining pubic tubercle and anterior superior iliac spine. Femoral artery is identified and then, the iliacus muscle covered by fascia iliaca is identified. The needle is advanced by in plane technique beneath the fascia iliaca and after negative aspiration, local anaesthetic is injected.FNB was given to patients in Group B. The femoral nerve was identified via the ultrasound probe placed at the level of the femoral crease distal to the inguinal ligament. The femoral nerve is found as a triangular hyper echoeic areas located lateral to the femoral artery, deep to the fascia iliaca on the anterior aspect of iliopsoas muscle. The femoral artery, being superficial is very easily visualized on ultrasound. In both groups, after identification of the targeted nerve and plane identification by ultrasound guidance, needle was advanced by in-plane technique. Initially 2 ml of local anaesthetic was injected to observe the spread of the drug. A total of 30 ml of 0.25% bupivacaine was injected after identification of needle tip and careful aspiration to rule out intravascular injection. Numerical rating scale (NRS) scores were used to assess

the pain. The NRS scale consists of a horizontal line with 0-10 markings, where score 0 is no pain, score 1-3 is mild pain, score 4-6 is moderate pain and score 7-10 is severe pain. The time interval between injection of local anaesthetic for FICB//FNB block and decrease in the pain scores to <3 was considered as onset of analgesia. The NRS pain scores at rest were recorded immediately before the study interventions and then at 3 mins, 5 mins, 10 mins, 15 mins and 30 mins after the block. Patients were monitored and observed for adverse effects and complications. Patients were then shifted to the operative room for anaesthetic and surgical management. Spinal anaesthesia was performed in sitting position 30 minutes after the study interventions i.e. FICB/FNB. The patient was blinded to the group allocation and the type of block technique they would undergo. The Anaesthesiologist performing the block tecnique as per group allocation was not further involved in the patient management and data collection. The anesthesiologist performing the spinal anaesthesia was blinded to the study drug and assessed the quality of patient positioning given scores as not satisfactory-0, satisfactory-1, good-2 and optimal-3. Data Analysis was done with assistance of Statistical expert. In patients who had pain with NRS pain scores >4 during positioning for spinal anaesthesia, supplemental analgesia was given with single dose of inj.fentanyl 50 μg IV.

Sample size calculation

The sample size calculation was based on a two-sample independent t-test, 90% power and a 5% two-sided significance level to demonstrate at least 25% differences in the NRS pain scores between the study groups based on a previous similar study (12). Total sample size required for the study was 90 (45 in each group).

Statistical analysis

The data were entered into an excel worksheet, and SPSS 20 was used for the analysis. Descriptive statistics were used**.** Data from categorical variables were provided in number (%) and results from continuous variables were presented as mean and SD. To determine the association between two categorical variables and continuous variables, chi-square test, paired t test, fischer's exact test, ANOVA, Mann –Whitney U test and independent t test were used. A p value of 0.05 or lower was regarded as statistically significant.

Ethical Approval

This was a randomized clinical study conducted at a tertiary care teaching hospital. The ethical committee of BLDEDU Shri BM Patil Medical College Hospital and Research Centre, Vijayapura was obtained (number: 09/2021 date:22/10/2021). The study was registered under the clinical trial registry of India-CTRI/2022/07/044334. The declaration of Helsinki recommendations was followed for the conduct of the study. Informed consent was obtained from all participants.

Results

The study was conducted on patients between 18-80 years who were undergoing elective surgery for proximal femur fractures. The two study groups were comparable in terms of demographic variables and no statistically significant differences were observed **(Table 1).**

Table 1. Demographic Data

Variables	Group A FICB (n=45)	Group B FNB (n=45)	p
Age (years) mean ± SD	53.76 ± 12.23	55.27 ± 11.37	0.54
Gender (Male: Female)	25:20	25:20	0.58
Weight (kg)	60.5 ± 9.1	60.6 ± 8.7	0.97
BMI (kg/m²)	25.89 ± 3.05	25.40 ± 2.34	0.41
ASA I/II/III	5/30/10	4/32/9	1.11
Intertrochanteric fracture,(%)	26 (57.77)	28 (62.22)	0.27
Neck of femur fracture,(%)	8 (17.77)	12 (26.66)	
Subtrochanteric fracture,(%)	2 (4.44)	2 (4.44)	
Proximal femur fracture,(%)	9 (20)	3 (6.66)	

Abbreviations: Data is represented by numbers and percentage (%), p value <0.05 is significance.

Time taken to perform the block was 8.52 ± 2.32 mins in Group A and 5.12 ± 1.22 mins in Group B **(**p < 0.001). The time taken was shorter in Group B and was statistically significant **(**Table 2). The onset of block was 4.3 ± 0.9 mins

in Group A and 2.8 ± 0.6 mins in Group B ($p < 0.001$). The onset of block was faster in Group B and was statistically significant **(Table 2).**

Table 2. Time required for block performance and onset of block

Variables	Group A FICB (n=45)	Group B FNB (n=45)	p
Time taken to perform USG block (minutes)	8.52 ± 2.32	5.12 ± 1.22	<0.001*
Time of Onset of block (minutes)	4.3±0.9	2.8±0.6	<0.001*

Patients who underwent blocks in group B had significant pain reduction during positioning. There was a statistically significant difference between the groups in terms of quality of patient positioning score with a p value of <0.001 (**Table 4).**

A score of 0 i.e. unsatisfactory positioning was observed in 5 (11.11%) patients in group A but none in group B. Best positioning with a score of 3 was observed in 15 (33.33%) patients in group A and in 32 (71.11%) patients in group B (**Table-3)**.

Table 3. Score for Quality of patient positioning

Score for Quality of patient positioning	Group A FICB (n=45), n(%)	Group B FNB (n=45), n(%)	p
0 (Not satisfactory)	5 (11.11)	0 (0)	<0.001*
1(Satisfactory)	6 (13.33)	1(2.22)	
2 (Good)	19 (42.22)	12 (26.67)	
3 (Optimal)	15 (33.33)	32(71.11)	

Abbeviations: Data is represented by numbers and percentages (%), p value <0.05* is significant

In study groups, NRS pain scores were recorded before the study intervention, at 3 mins, and 5 mins, and p-values were 0.919, 0.925, and 0.611, respectively, showing no statistically significant difference between the groups**.** At 10 minutes, NRS pain scores of 4–6 were seen in 11 patients in Group A and 2 patients in Group B. Severe pain with NRS scores of 7–10 were seen in 3 patients of Group A, whereas none in Group B. At 15 minutes, NRS scores of 4–6 were seen in 7 patients of Group A and none in Group B. Severe pain with NRS scores of 7–10 was seen in 1 patient of Group A and none in Group B. At 30 minutes, NRS scores of 4–6 were seen in 4 patients of Group A and none in Group B. Severe pain with NRS scores of 7–10 was seen in 1 patient of Group A and none in Group B. NRS pain scores between the study groups at 10 mins, 15 mins, and 30 mins after intervention showed a statistically significant difference between the groups**,** with p-values of 0.018, 0.02, and 0.02, respectively **(Table 4)**.

Table 4. NRS Pain scores

Time	NRS scores	Group A FICB (n=45) n(%)	Group B FNB (n=45) n(%)	p
Before block	0	1 (2.22)	1 (2.22)	0.919
	1-3	8 (17.78)	10 (22.22)	
	4-6	11 (24.44)	13 (28.89)	
	7-10	25 (55.56)	21 (46.67)	
3 mins	0	5 (11.11)	4 (8.89)	0.925
	1-3	11 (24.44)	15 (33.33)	
	4-6	19 (42.22)	17 (37.78)	
	7-10	10 (22.22)	9 (20)	
5 mins	0	11 (24.44)	15 (33.33)	0.611
	1-3	19 (42.22)	17 (37.78)	
	4-6	10 (22.22)	9 (20)	
	7-10	5 (11.11)	4 (8.89)	
10 mins	0	20 (44.44)	24 (53.33)	0.018
	1-3	11 (24.44)	15 (33.33)	
	4-6	11 (24.44)	2 (4.44)	
	7-10	3 (6.67)	0	
15 mins	0	30 (66.67)	40 (88.89)	0.021
	1-3	7 (15.56)	5 (11.11)	
	4-6	7 (15.56)	0	

	7-10	1 (2.22)	0	
30 mins	0	30 (66.66)	40 (88.88)	0.022
	1-3	10 (19.55)	5 (22.22)	
	4-6	4 (10.55)	0	
	7-10	1 (2.22)	0	

There were no incidences of complications such as bleeding/hematoma at the site of the block, adverse systemic toxicity, nausea, vomiting, hypotension, bradycardia, or respiratory depression in either of the two study groups. Supplemental analgesia with fentanyl was not given to 40 patients in Group A and all patients in Group B. In five patients in Group A, fentanyl 50 μg IV was given prior to positioning for spinal anaesthesia..

Discussion

Proximal femur fractures cause significant distress to patients during positioning for spinal anaesthesia. Regional nerve blocks like FNB and FICB can be used as adjuvant techniques for reducing pain, thereby helping to optimize patient positioning for successful spinal anaesthesia. Fan X et al. (8) in a meta-analysis compared the efficacy of Fascia iliaca compartment block and femoral nerve block for pain management in hip surgeries. They observed that these regional anaesthesia techniques were effective for pain control for proximal femur fractures.USG guided peripheral nerve blocks have the advantages of direct visualization of the nerve or neuraxial structures, surrounding vascular structures, needle tip position and spread of local anaesthetic solution thus allowing optimal placement of the local anaesthetic and minimising the procedure related complications, especially the devastating intravascular injections (13,14). Commonly used systemic analgesics are opioids, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Safe and effective doses of opioids and NSAIDs are difficult to titrate in the post- traumatic patients, especially the geriatric population (15,16,17). Femoral nerve block (FNB) is being used for analgesia in femur fractures in the emergency department. The femoral nerve is a terminal branch of the lumbar plexus arising from the ventral rami of the second, third and fourth lumbar nerves.

Femoral nerve block results in anaesthesia of the skin of the antero-medial thigh, knee and the medial border of the leg. (18,19). The muscles innervated by the femoral nerve are the sartorius, quadriceps femoris, iliopsoas and pectineus muscles. The femoral nerve innervates the anterior aspects of the hip joint, the anterior aspect of the femur and the anteromedial aspects of the knee joint (20). The femoral nerve can be easily located at the level of inguinal crease where it is superficially situated. Femoral nerve blockades by landmark technique lateral to the femoral artery pulsations have high failure rates and complications. Spinal anaesthesia is a commonly preferred technique by anaesthesologists worldwide for lower limb orthopedic surgeries. Positioning a patient with hip and femur fractures for spinal anaesthesia causes excruciating pain. Adverse effects of pain include tachycardia, hypertension and compromised myocardial blood flow. Mismanagement of acute pain is an independent risk factor for chronic persistent post-surgical pain (21,22). Our present study was to compare the analgesic efficacy of ultrasound-guided FNB and FICB in patients with proximal femur fractures to minimise pain associated with positioning for spinal anaesthesia. Sandby-Thomas et al. (15) in their research on perioperative care of femur fractures observed that during patients' positioning for subarachnoid block, midazolam, ketamine and propofol were the commonly used systemic agents.

They reported that to aid positioning, nerve blocks were used very infrequently and any sedation or analgesia was not being given in around 15.1% of patients. National Institute for Health and Clinical Excellence regulations recommend that nerve blocks be taken into account to minimize opioid dose and provide additional analgesia (21). Newman et al (22) used a nerve stimulator guided nerve blocks and observed a mean post-block VAS score of 4.4 for FNB and a score of 5.4 for FICB using 0.5% levobupivacaine with a statistically significant difference. In our study with ultrasound guidance block we observed effective analgesia with FNB and FICB and both blocks were equally efficacious and an 8- 10-minute interval after the block was sufficient to provide adequate analgesia to proceed to spinal anaesthesia in all the patients. Callear et al (16) in a non-comparative study, using landmark technique observed that the FICB, using 30 mL of 0.25% bupivacaine, reduced pain considerably 15 minutes after the block was given. Similarly, Kumar et al (23) in their study observed that using 30 mL of 0.5% ropivacaine given to a FICB to relieve pain before positioning for spinal anaesthesia was assessed 20 minutes after the block, VAS score was reduced to 2.94 with ~~a~~ $p < 0.01$, which showed significance statistically. Jain N et al. (12) also observed that FNB had better pain reduction with significantly less VAS score than FIB post block. Ultrasound-guided

bupivacaine deposition in the vicinity of the femoral nerve which also innervates the hip and femur joint increases the possibility of nerve blockage. This might explain why FNB is more effective in providing analgesia than FICB.
In the present study, we observed that with FNB there was improved patient positioning in comparison to FICB. In the FNB group, there were 32 (71.11%) patients who had optimal positioning while in the FICB group only 15 (33.33%) patients had optimal positioning. Statistically, FNB group patients had better positioning scores than patients in the FICB group.
There were no incidences of complications like bleeding/hematoma at the site of the block, adverse systemic toxicity, nausea, vomiting, hypotension, bradycardia, or respiratory depression either of the two study groups. This can be attributed to the use of an ultrasound-guided block in comparison to the anatomical landmark approach. Previous studies also suggested that ultrasound-guided blocks are safe, have decreased onset time and are more effective than the anatomical landmark approach or nerve stimulator approach. Ultrasound guidance is a better tool for visualizing anatomical features during nerve block administration and may be utilized for performing FNB and FICB (20).

Limitations

Larger sample size and multicenter trials are required to validate the findings and improve the generalizability of the study. NRS score was used for pain score which is subjective and pain threshold may vary in each individual.

Conclusion

Both the FNB and the FICB using ultrasound guidance are simple and effective techniques. In our study patients in the group B (FNB) had lower NRS scores compared to group A(FICB). Ultrasound-guided FNB may offer faster onset of block and better pain relief than FICB for assisting with optimum positioning for spinal anaesthesia in patients with proximal femur fractures.

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Ethical Approval: *This Study approval was obtained from the Institutional Ethics Committee of the BLDEDU Shri BM Patil Medical College Hospital and Research Centre, Vijayapura (number: 09/2021 date 22/10/2021). Informed consent was obtained from all participants.*
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Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research. authorship and/or publication of this article.*
Data Availability: *The data used to support the findings of this study are available from the corresponding author upon request*
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Original Article

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What do Orthodontists Think About the Diagnosis and Treatment Plan of Patients with Class II Division 1 Skeletal Anomalies? A Preliminary Study

Ortodontistler Sınıf II Bölüm 1 İskelet Anomalisi Olan Hastaların Teşhis ve Tedavi Planı Hakkında Ne Düşünüyor? Bir Ön Çalışmasıı

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Abstract

This stud aimed to determine key diagnostic approaches and treatment preferences among orthodontists treating adult patients with Class II Division 1 skeletal anomalies.

Materials and Methods: A total of 50 orthodontists participated in this survey-based study.

Ten structured questions were asked regarding diagnostic methods and treatment choices, including bracket systems, torque preferences, imaging techniques, space-creating methods, tooth extraction preferences, malocclusion treatment approaches, and retention strategies. Statistical analyses were performed using chi-square tests for categorical variables, and a p-value < 0.05 was considered statistically significant.

Results: Among the participants, 64% preferred traditional braces, while 24% used self-ligating braces. Regarding prescription selection, 56% used **McL**aughlin, **B**ennett, **T**revisi, 24% Roth, and 20% other systems. Standard torque brackets were preferred by 84% of respondents. For diagnosis, 64% used cephalometric tomography, while 24% relied solely on computed tomography. The most common space-creating approach was distalization (72%), and the most frequently extracted teeth were the upper third molars (52%). The majority (64%) preferred intermaxillary elastics combined with mini-implants for occlusal correction. For retention, 50% used both fixed and removable retainers.

Chi-square analysis (showed) statistically significant associations between years of clinical experience and appliance choice ($p < 0.05$), as well as between diagnostic modality and preference for surgical versus non-surgical treatment plans ($p < 0.05$).

Conclusions: The study highlights the diversity in orthodontic diagnosis and treatment planning. Most orthodontists favored modern, non-surgical approaches, emphasizing efficiency in treatment duration while balancing aesthetics and functional outcomes.

Keywords: Class II Division 1, computed tomography, fixed functional appliances, orthodontic survey, retention

ÖZ

Amaç: Bu çalışma, Sınıf II Bölüm 1 iskeletsel anomalileri olan yetişkin hastaları tedavi eden ortodontistler arasındaki temel tanısal yaklaşımları ve tedavi tercihlerini belirlemeyi amaçlamıştır.

Gereç ve Yöntem: Bu ankete dayalı çalışmaya toplam 50 ortodontist katılmıştır. Braket sistemleri, tork tercihleri, görüntüleme teknikleri, yer açma yöntemleri, diş çekimi tercihleri, maloklüzyon tedavi yaklaşımları ve retansiyon stratejileri dahil olmak üzere teşhis yöntemleri ve tedavi tercihleri ile ilgili on yapılandırılmış soru yöneltilmiştir. İstatistiksel analizler kategorik değişkenler için ki-kare testleri kullanılarak yapılmış ve $p < 0.05$ istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Katılımcıların %64'ü geleneksel diş tellerini tercih ederken, %24'ü kendinden bağlanan diş tellerini tercih etmiştir. Tedavi sistem seçiminde %56'sı MBT, %24'ü Roth ve %20'si diğer sistemleri seçmiştir. Standart tork braketleri katılımcıların %84'ü tarafından tercih edilmiştir. Teşhis için %64'ü sefalometrik tomografi kullanırken, %24'ü yalnızca bilgisayarlı tomografiye güvenmiştir. En yaygın yer açma yaklaşımı distalizasyondu (%72) ve en sık çekilen dişler üst üçüncü molarlardı (%52). Çoğunluk (%64) oklüzal düzeltme için mini implantlarla birlikte intermaksiller lastikleri tercih etmiştir. Retansiyon için %50'si hem sabit hem de hareketli retainer kullanmıştır.

Sonuçlar: Bu çalışma ortodontik tanı ve tedavi planlamasındaki çeşitliliği vurgulamaktadır. Çoğu ortodontist modern, cerrahi olmayan yaklaşımları tercih etmiş, estetik ve fonksiyonel sonuçları dengelerken tedavi süresinde verimliliği vurgulamıştır.

Anahtar Kelimeler: Sınıf II Bölüm 1, ortodontik anket, sabit fonksiyonel apareyler, bilgisayarlı tomografi, retansiyon

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Highlights

- Traditional braces and McLaughlin, Bennett, Trevisi were most preferred.
- Non-extraction approaches with distalization dominated.
- Combined fixed and removable retainers were common.

Introduction

According to Edward Angle, Class II malocclusion is characterized by the mesiobuccal cusp of the upper first molars being located more mesially than the mesiobuccal fissure of the lower first molars, distoocclusion (1,2). Class II malocclusion is one of the most common developmental anomalies, with a prevalence of 15–30% in most populations (2,3), and can lead to serious adverse social, psychological, and aesthetic consequences (4,5). This dentoalveolar anomaly can be divided into two different categories depending on the deficiency of the mandible or the excess development of the maxilla (6,7). This anomaly may present with varying degrees of Class II malocclusion at different ages, which determines the preferred approach in clinical treatment (8).

Class II malocclusion can be divided into two types based on the position of the upper incisors. The most important feature of Class II division 1 malocclusion, which varies between 5-29% in prevalence, is labially inclined upper incisors and increased overjet. This condition may be accompanied by a narrow upper dental arch. Incisor occlusion may vary between deep bite and open bite (8). In Class II Division 2 malocclusion, with a reported prevalence ranging between 1.5% and 11% (5,10–12), the upper incisors are generally retroclination and the mandibular first molars are positioned further back than the upper first molars (13,14). This condition is often accompanied by a deep bite and reduced overjet. Protrusion of the upper incisors or protrusion of the lower incisors due to habits or soft tissues may result in increased overjet regardless of skeletal relationships (9). Individuals with class II division 1 malocclusion often have inadequate lips to perform the task and attempt to compensate through peripheral muscle activity, by rolling the lower lip behind the upper incisors or by moving the tongue forward between the incisors, or through a combination of these elements (9). Thumb sucking or other habits may lead to the development of this malocclusion, often by creating imbalances between the buccinator muscles and tongue force, which narrows the maxillary arch. In addition, these habits often direct the upper incisors forward and the lower incisors backward. Dental characteristics such as tooth size and arch length differences may play a role in the development of class II malocclusion, in which labial movement of the upper incisors may cause increased overjet (9,20). Factors affecting the etiology of malocclusion can be examined in four groups as skeletal, dental, local and soft tissues (3,15-17).

As with other types of malocclusion, class II malocclusion can be diagnosed by clinically accurate assessment of the patient (extraoral and intraoral features), using correct diagnostic tools (anamnesis, photographic analysis, radiographic analysis and plaster analysis) and performing correct functional analysis (postural rest position, maximum intercuspation, temporomandibular joint and orofacial dysfunction examination) (18, 19). Class II malocclusion is defined when the mesiobuccal cusp of the upper permanent first molar is positioned mesially from the mesial fissure of the lower permanent first molar by more than half of its width (12). Patients with class II division 1 malocclusion usually have a convex profile, dolichocephalic head shape, deepened mentolabial sulcus, and mental muscle activity (11, 18). Morphologically different structures or teeth that are inclined mesially/distally may lead to misinterpretation of class II malocclusion (10). The components of skeletal class II malocclusion can be classified according to the maxillo-mandibular jaw relationship, skull base size, vertical dimension discrepancy and occlusion plane status (10).

Skeletal Class II anomalies are characterized by mandibular deficiency of 80%, maxillary excess of 20% or posterior positioning of the condyle within the glenoid fossa (19). In patients with growth potential, mandibular deficiency can be treated with fixed or removable functional appliances that change the anteroposterior and vertical positions of the mandible, reshape the condyle and stimulate mandibular growth. In addition, headgears are used to restrict or redirect growth in the maxilla in Class II patients with maxillary excess and growth potential (19). In individuals with completed craniofacial growth, treatment options include intraoral or extraoral distalization appliances, tooth extractions, and orthognathic surgery to skeletal Class II anomalies. Factors such as the origin of the anomaly maxillary or mandibular factors such as the severity of the discrepancy, the patient's growth stage, growth potential, and soft tissue profile are also considered in treatment planning (20).

Consequently, treatment strategies are tailored to these individual factors. Surveys are structured instruments used to collect information on individuals' attitudes, perceptions, experiences, and preferences (20). Considering the difficulties encountered during the COVID-19 pandemic and quarantine period while collecting data, survey studies have gained importance.

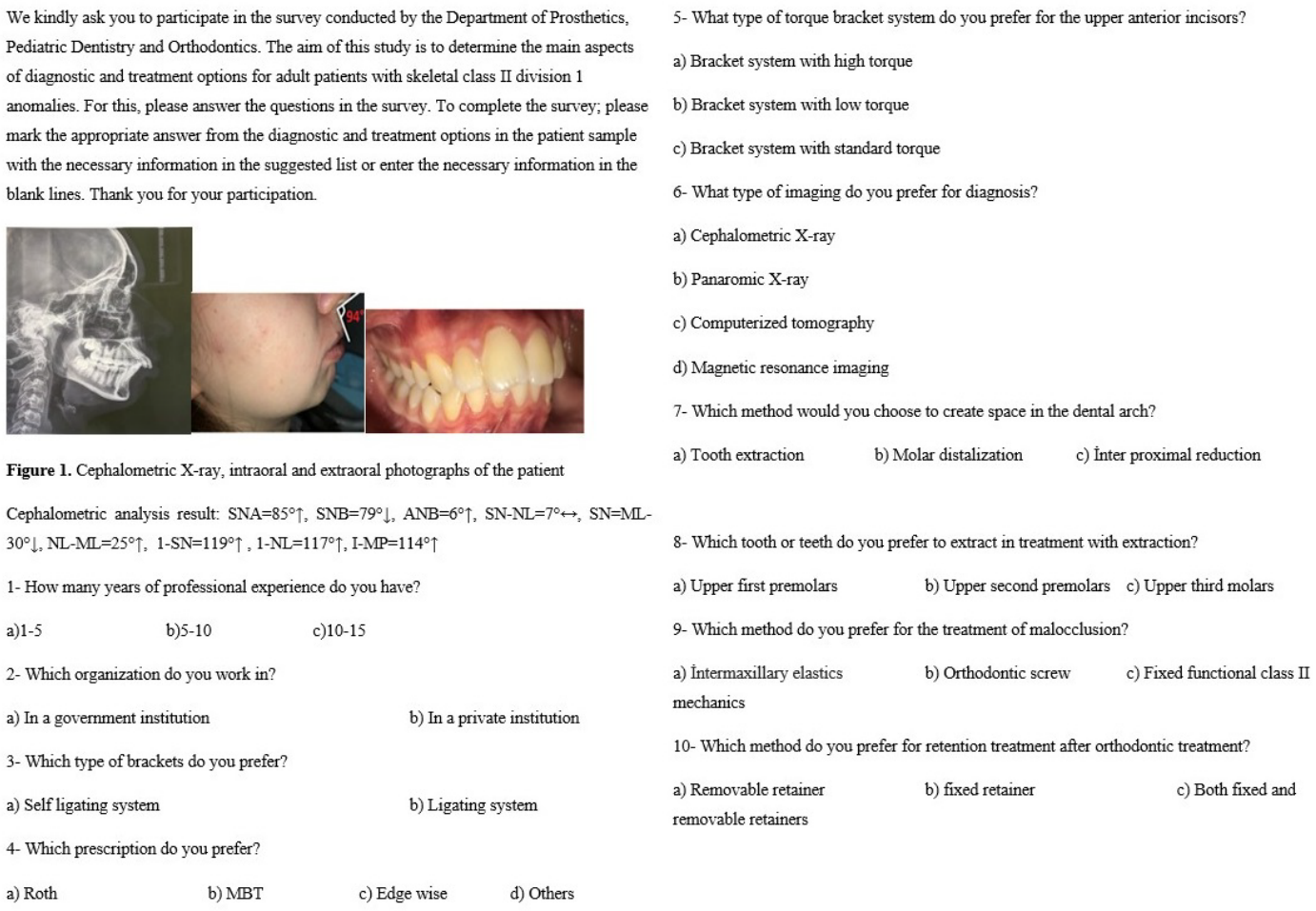
This study aimed to evaluate the diagnostic methods and treatment preferences of orthodontists managing adult patients with Class II Division 1 skeletal malocclusions, focusing on bracket systems, torque selection, imaging techniques, space creation, extraction patterns, correction strategies, and retention protocols. Additionally, it assessed associations between clinical experience, diagnostic choices, and treatment decisions.

Material and Methods

Study design and data collection

This was a preliminary cross-sectional survey study. While preparing the questions, the most frequently used and up-to-date techniques in the diagnosis and treatment of (Class II Division 1 skeletal anomalies) in the literature were taken into consideration. The survey included questions on years of clinical experience, workplace type (public or private), bracket system preference, prescription type selection, torque selection for maxillary incisors, preferred imaging method, space-creating technique, tooth extraction choices (if applicable), malocclusion treatment methods, and retention strategies.

A printed survey consisting of 10 questions was randomly distributed to 64 certified orthodontists who received training in the Republic of Belarus, and 50 of them completed the survey. Participants were randomly selected regardless of gender or professional experience. Informed consent was obtained from the participants. The data collection period was set at 3 months. **(Figure 1)**



We kindly ask you to participate in the survey conducted by the Department of Prosthetics, Pediatric Dentistry and Orthodontics. The aim of this study is to determine the main aspects of diagnostic and treatment options for adult patients with skeletal class II division 1 anomalies. For this, please answer the questions in the survey. To complete the survey; please mark the appropriate answer from the diagnostic and treatment options in the patient sample with the necessary information in the suggested list or enter the necessary information in the blank lines. Thank you for your participation.

Figure 1. Cephalometric X-ray, intraoral and extraoral photographs of the patient

Cephalometric analysis result: SNA=85°↑, SNB=79°↓, ANB=6°↑, SN-NL=7°↔, SN=ML-30°↓, NL-ML=25°↑, 1-SN=119°↑ , 1-NL=117°↑, I-MP=114°↑

1- How many years of professional experience do you have?

a)1-5 b)5-10 c)10-15

2- Which organization do you work in?

a) In a government institution b) In a private institution

3- Which type of brackets do you prefer?

a) Self ligating system b) Ligating system

4- Which prescription do you prefer?

a) Roth b) MBT c) Edge wise d) Others

5- What type of torque bracket system do you prefer for the upper anterior incisors?

a) Bracket system with high torque

b) Bracket system with low torque

c) Bracket system with standard torque

6- What type of imaging do you prefer for diagnosis?

a) Cephalometric X-ray

b) Panaromic X-ray

c) Computerized tomography

d) Magnetic resonance imaging

7- Which method would you choose to create space in the dental arch?

a) Tooth extraction b) Molar distalization c) İnter proximal reduction

8- Which tooth or teeth do you prefer to extract in treatment with extraction?

a) Upper first premolars b) Upper second premolars c) Upper third molars

9- Which method do you prefer for the treatment of malocclusion?

a) İntermaxillary elastics b) Orthodontic screw c) Fixed functional class II mechanics

10- Which method do you prefer for retention treatment after orthodontic treatment?

a) Removable retainer b) fixed retainer c) Both fixed and removable retainers

Figure 1: Survey sample

Sample size determination and statistical analysis

The study determined the necessary sample size using a priori power analysis by G*Power software (ver. 3.1.9.4; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) (21). To determine the required sample size and ensure the study's statistical power, a power analysis was conducted with the following parameters: Incidence in the general population: 78%, Incidence in the study group: 64%, Alpha (Type I error probability): 0.05, Beta (Type II error probability): 0.2, Statistical power: 0.8, Required sample size (N): 75.

While the sample size of 50 orthodontists was slightly below the ideal 75, the statistical power of 0.8 was considered sufficient for detecting true differences in treatment preferences. Future studies with a larger sample size would enhance the reliability and generalizability of the findings. Statistical analyses were performed using the chi-square test for categorical data, and $p < 0.05$ were considered statistically significant.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of the Belarusian Medical Academy of Post-Graduate Education (Approval number: 109, dated 19.07.2021). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants

Results

A summary of orthodontists' preferences in diagnosing and treating Class II Division 1 malocclusion is presented in **Table 1**. Most respondents were early-career professionals working in public institutions and favored traditional braces and the MBT prescription system. Standard torque brackets and cephalometric tomography were commonly used for diagnosis. Molar distalization was the preferred method for space creation, while upper third molars were the most frequently extracted teeth. For retention, a combination of fixed and removable retainers was the most commonly used approach, emphasizing individualized post-treatment care.

A Figure visualizing orthodontists' preferences in diagnosing and treating Class II Division 1 malocclusion based on the survey data is presented in **Figure 2**. It highlights various factors such as clinical experience, workplace setting, treatment choices, and retention strategies.

Table 1. Summary of orthodontists' preferences in the diagnosis and treatment of Class II Division 1 malocclusion, including clinical experience, treatment modalities, and retention strategies.

Category	Preference / Outcome	Percentage (%)
Clinical Experience	1–5 years	58
	5–10 years	32
	10–15 years	10
Workplace	Public institution	76
	Public & private sector	24
Bracket System	Traditional braces	64
	Self-ligating braces	24
	Both	12
Prescription Type	MBT	56
	Roth	24
	Other	20
Torque Selection	Standard torque brackets	84
Imaging Method	Cephalometric tomography	64
	Computed tomography	24
Space-Creation Approach	Molar distalization	72
Tooth Extraction	Upper third molars	52
Occlusion Correction	Intermaxillary elastics with mini-implants	64
Retention Strategy	Fixed & removable retainers	50
	Fixed retainers only	30

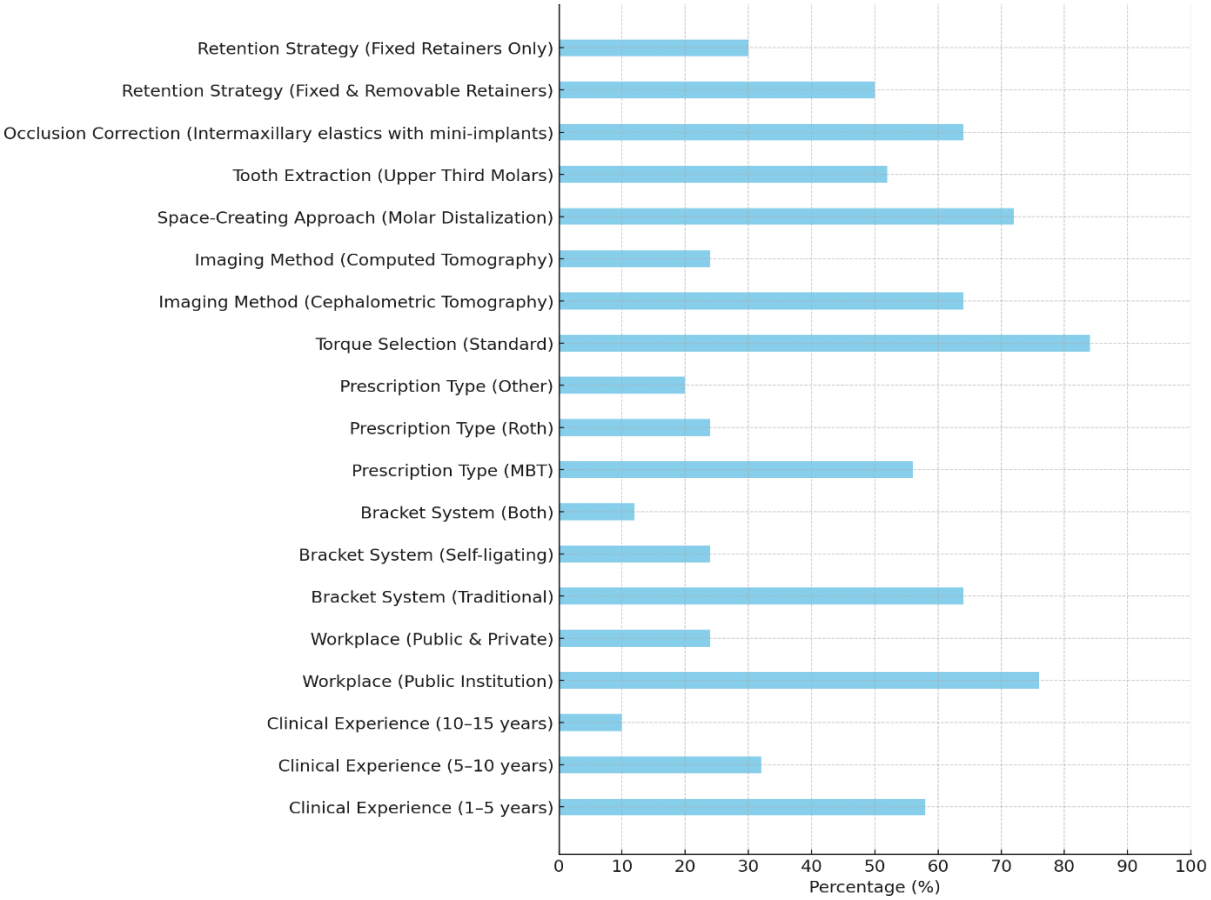


Figure 2. Orthodontists' Preferences in the Diagnosis and Treatment of Class II Division 1 Malocclusion (Chi-square Analysis)

Discussion

The findings indicate a preference for modern, non-surgical approaches in the treatment of Class II Division 1 malocclusion. Traditional bracket systems, MBT prescriptions, and standard torque brackets remained dominant choices. Imaging modalities, particularly cephalometric tomography, played a critical role in diagnosis. For space creation and occlusal correction, molar distalization and mini-implants were frequently preferred. Retention strategies varied, with an equal distribution between fixed and removable retainers.

More conservative and patient-friendly treatment modalities, minimizing invasive procedures while maintaining efficiency and aesthetic outcomes. The statistical significance of these findings ($p < 0.05$) reinforces the reliability of the observed trends.

Recent research has emphasized the role of skeletal anchorage systems in optimizing outcomes for Class II Division 1 patients. Temporary anchorage devices (TADs) have been shown to improve distalization efficiency, reduce the need for premolar extractions, and provide more stable long-term occlusal results (2). This aligns with our findings, where mini-implants were commonly employed for occlusion correction.

Similarly, advances in three-dimensional imaging have improved diagnostic precision. Cone-beam computed tomography (CBCT) enables more accurate assessment of skeletal discrepancies and airway dimensions, thereby facilitating personalized treatment planning (22). Although cephalometric tomography was predominantly used among our respondents, wider integration of CBCT could further refine clinical decision-making.

Long-term stability remains a major concern in Class II Division 1 management. Meta-analyses suggest that functional appliance therapy combined with fixed orthodontics produces more stable results than fixed appliances alone (23). This highlights the importance of incorporating functional orthopedic interventions during early treatment to optimize stability and reduce relapse risks. Nonetheless, studies have found no significant differences between early (two-stage) and late treatment outcomes (24). Regarding extraction therapy, Booij et al. (25) demonstrated stable results with first permanent molar extraction, while most participants in our study preferred first premolar extraction. Although self-ligating systems were chosen by many participants, Maizeray et al. (26) reported no significant clinical differences between self-ligating and conventional brackets.

Future research should emphasize the integration of digital workflows and artificial intelligence-driven diagnostic tools to improve efficiency and predictability. Expanding studies to include larger, multinational cohorts would also help diversify perspectives and enhance generalizability. Longitudinal designs are necessary to assess relapse rates and long-term stability.

In conclusion, this study highlights the ongoing evolution of diagnostic and therapeutic strategies for Class II Division 1 malocclusion. The preference for modern, minimally invasive approaches reflects a growing emphasis on patient comfort, aesthetics, and treatment efficiency. The paradigm shifts toward molar distalization supported by skeletal anchorage systems underscores the move away from extractions. Importantly, individualized treatment planning—considering patient age, growth potential, and soft tissue characteristics—remains central to successful outcomes. Although the limited sample size and geographic scope warrant caution in interpretation, these findings provide valuable insight into current trends. Moreover, the integration of artificial intelligence and digital workflow technologies could further enhance diagnostic accuracy, improve treatment efficiency, and standardize care

Study limitations

This preliminary study has certain limitations. The relatively small sample size (n=50) reduces statistical power and limits the generalizability of the findings**.** Furthermore, all participants were orthodontists trained in a single country**,** which may not capture global variations in diagnostic and treatment approaches. The reliance on self-reported survey data may also introduce recall bias and subjective interpretation. Finally**, as** this study provides only a cross-sectional snapshot, future multi-center and longitudinal studies with larger cohorts are required to validate these findings and assess long-term treatment stability**.**

Conclusion

In conclusion, this study highlights evolving trends in the management of Class II Division 1 malocclusion**,** emphasizing modern, patient-centered, and minimally invasive approaches. The findings suggest that integrating advanced imaging, skeletal anchorage systems, and digital technologies can enhance diagnostic precision and treatment efficiency while reducing reliance on extractions and surgical procedures. Future studies should validate these results through larger, multi-center, and longitudinal studies to assess long-term stability**.** Moreover, the incorporation of artificial intelligence in treatment planning holds promise for more accurate and predictive outcomes. Ongoing refinement of diagnostic and therapeutic strategies will be essential to optimize results and maintain a strong focus on patient-centered care.

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Ethical Approval: *This Study approval was obtained from the Institutional Ethics Committee of the Belarussian Medical Academy of Post-Graduate Education institution (number: 109 date :19.07. 2021). Informed consent was obtained from all participants***.**
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Original Article

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Tear Carnitine Analysis After Corneal Crosslinking in Keratoconus

Keratokonus'ta Korneal Crosslinking Sonrasi Gözyaşi Karnitin Analizi

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Abstract

Background: This study aimed to investigate changes in carnitine levels after CXL treatment, which play an important role in the cell's energy cycle

Materials and Methods: Single eye of 25 patients who underwent crosslinking (CXL) therapy for keratoconus were included in this prospective, nonrandomized study. Patients were divided into 4 different groups based on gender (male/female) and age (<18/≥18) before treatment. Tears were collected with capillary tubes before, and at the 6th postoperative month without anesthetic. From the tear samples, 27 carnitine ester parameters were measured by a mass spectrometer and an ultra-high-performance liquid chromatograph (UHPLC).

Results: The average age of patients comprising **11** (44%) men and 14 (66%) women were 18.28 ± 3.98 years (12-25). After CXL treatment, statistically significant changes were only detected in C12 (Dodecanoyl Carnitine) and C14 (Myristoyl Carnitine) levels. Among all carnitines, only C4 and C6 carnitine levels increased, but this increase was not statistically significant. Among the age groups, the highest difference was in carnitine derivative C6, and the least differing carnitine derivative was C51 and C5DC. The carnitine derivatives that differed most between genders were C6 and C16, while the least differed were C5DC and C8:1. **Conclusions:** In cases where energy needs increase, such as inflammation, there may be a decrease in inflammation severity as carnitine levels decrease. The variation between pre and post CXL carnitine level measurements in keratoconus patients can be used as a useful marker to monitor inflammation and intervene in the event of excessive inflammation.

Keywords: Acylcarnitine; Carnitine; Crosslinking; Keratoconus; Metabolomics.

ÖZ

Amaç: Hücrenin enerji döngüsünde önemli rol oynayan karnitin düzeylerinde CXL tedavisi sonrası oluşabilecek değişiklikleri araştırmak.

Gereç ve Yöntem: Bu prospektif, randomize olmayan çalışmaya keratokonus nedeniyle çapraz bağlama (CXL) tedavisi uygulanan 25 hastanın tek gözü dahil edildi. Hastalar tedavi öncesi erkek, kadın, 18 yaş üstü ve 18 yaş altı olmak üzere 4 farklı gruba ayrıldı. Gözyaşları ameliyat öncesi ve ameliyat sonrası 6. ayda herhangi bir anestezik madde kullanılmadan kılcal tüplerle toplandı. Gözyaşı örneklerinden 27 karnitin ester parametresi bir kütle spektrometresi ve bir ultra yüksek performanslı sıvı kromatografı ile ölçüldü. **Bulgular:** 11'i (%44) erkek, 14'ü (%66) kadından oluşan hastaların yaş ortalaması 18,28 ± 3,98 yıl (12-25) idi. CXL tedavisi sonrasında sadece C12 (Dodecanoyl Carnitine) ve C14 (Myristoyl Carnitine) düzeylerinde istatistiksel olarak anlamlı değişiklikler tespit edildi. Tüm karnitinlerden sadece C4 ve C6 karnitin düzeylerinde artış görüldü ancak bu artış istatistiksel olarak anlamlı değildi. Yaş grupları arasında en yüksek farklılık karnitin türevi C6'da görülürken, en az farklılık gösteren karnitin türevi ise C51 ve C5DC oldu. Cinsiyet gruplarında en fazla farklılık gösteren karnitin türevleri C6 ve C16 olurken, en az farklılık gösterenler ise C5DC ve C8:1 oldu.

Sonuç: İnflamasyon gibi enerji ihtiyacının arttığı durumlarda karnitin düzeyleri azaldıkça inflamasyon şiddetinde de azalma olabilir. Keratokonus hastalarında CXL öncesi ve sonrası karnitin seviyesi ölçümleri arasındaki farklılık, bu inflamasyonun izlenmesi ve aşırı inflamasyon durumunda müdahale edilmesi için yararlı bir belirteç olarak kullanılabilir

Anahtar kelimeler: Açilkarnitin, Karnitin, Crosslinking, Keratokonus, Metabolomics

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Highlights

- Carnitine, which plays an important role in the metabolism of fatty acids in the cell.
- A significant decrease in dodecanoyl carnitine and myristoyl carnitine levels was found secondary to the regression of inflammation after CXL treatment.
- Among all carnitines, only C4 and C6 carnitine levels increased.

Introduction

Corneal collagen crosslinking (CXL) treatment is the only treatment method known to stop or slow the progression of keratoconus(1). After this treatment, which creates new covalent bonds between amino acids in collagen fibrils through reactive oxygen radicals, corneal biomechanical resistance and stability increase (2). After CXL treatment, changes occur in fibroblasts of the corneal stroma, and these changes have been identified as markers of treatment efficacy (3). Although biochemical reactions occur mainly in the stroma during this treatment, some changes may occur on the ocular surface and in the tear film (4,5). In addition, the content of the tear film can also be an indicator of the metabolic functions of the cornea (3,6). athological processes occurring in corneal tissue may cause changes in the metabolome, leading to increased or decreased metabolites (7). Metabolomics, including carnitine, can be detected in many body fluids using mass spectrometry (8). Carnitine, a quaternary, non-essential amino acid, is synthesized from essential amino acids lysine and methionine. Carnitine, which plays an important role in the metabolism of fatty acids in the cell, is a quaternary ammonium compound. Carnitine plays a role in the transport of fatty acids to mitochondria and β-oxidation by binding to long-chain fatty acids as acyl residues (9,10). Thus, this study aims to investigate the changes that may occur after CXL treatment in carnitine levels, which has an important role in the cell's energy cycle.

Material and Methods

Study design

The diagnosis of keratoconus was made according to the criteria defined by Rabinowitz et al. (11). One eye of 25 patients who underwent crosslinking therapy for keratoconus was included in this prospective, nonrandomized study. The cases were selected from patients with keratoconus who were admitted to the Cornea Department of Harran University Faculty of Medicine.

atients with an increase in Kmax of more than 1 dioptre in the last two follow-up examinations performed at 6-month intervals were evaluated as progressive keratoconus. The following patients were excluded from the study: those with the thinnest corneal thickness less than 400 μm, corneal scar or infection, uveitis, glaucoma, ocular trauma, history of contact lens use, autoimmune disease, pregnancy, lactation, previous ocular surgery, and those with a history of topical/systemic immunosuppressive or steroid use.

s the surgical technique, conventional CXL (Dresden Protocol) was performed (12). Following topical anesthesia with 0.5% proparacaine hydrochloride, a 9.0 mm central epithelial debridement was performed with 20% alcohol as keratectomy.

Riboflavin instillation was initiated with a solution containing 0.1% riboflavin + 20% dextran T500 (Collagex, Taipei, Taiwan), applied at 2-minute intervals for 30 minutes. Corneal thickness was measured with an ultrasonic pachymeter before ultraviolet A (UVA) application and was confirmed to be over 400 μm. For the next 30 minutes, UVA was applied with LightLink-CXL (LIGHTMED, Taiwan) at 365 nm and 3.0 mW/cm², and riboflavin instillation was continued at 2-minute intervals during the procedure.

ontact lenses were placed after the procedure. Topical antibiotics were used 4 times a day for 1 week (0.05% moxifloxacin, Moxai® Abdi Ibrahim). After the epithelium had healed, topical steroid treatment was started 4 times a day, then tapered after 2 weeks and continued for 3 months (0.5% loteprednol etabonate, Lotemax®, Bausch + Lomb).

Tears were collected with capillary tubes as defined by Posa et al. (13) before and at the 6th postoperative month without any anesthetic agent. Collected tears were kept at -80°C until the date of analysis. Patients were divided into four groups based on gender (male/female) and age (<18/≥18) before treatment.

Laboratory analysis

Chemicals and Reagents

The reagents used were the internal standard set of Labeled Carnitine Standards-Set B from Cambridge Isotope Laboratories (UK). Mobile phase modifiers such as formic acid and acetonitrile were used in combination with high-performance liquid chromatography (HPLC) gradient-grade methanol (J.T. Baker, Center Valley, PA, USA) and deionized water (Millipore Simplicity UV water purification system, Waters Corporation, Milford, MA, USA).

LC-MS / MS carnitine determination

From the tear samples, 27 carnitine ester parameters were measured by a Shimadzu-8040 triple-quad mass spectrometer (MS/MS) (Shimadzu-8040) and a Shimadzu Nexera X2 ultra-high-performance liquid chromatograph (UHPLC). The carnitine profile was studied by modifying the neonatal screening method developed by LaMarca and Azzari (19,20). Filter paper (Whatman filter paper 10538018), cut into 3.2 mm discs, was placed in 96 well plates. 5 μL of tear samples was then placed in each well and allowed to dry at room temperature overnight. Sample extraction was performed using a methanol mixture of approximately 66.6%/33.3% (v/v) and a 300 μL extraction solution of 3 mmol/L hydrazine hydrate aqueous solution, respectively. The extraction solution included internal standards and several stable heavy isotope analogs of carnitine and acylcarnitines. The extracted sample was injected into the Shimadzu LCMS-8040. Mass spectral data for amino acids were obtained using a neutral loss scan of 46 Da in positive mode (CE = 15 V). Mass spectral data for acylcarnitines were obtained using an 85 m/z precursor ion scan in positive mode (CE = 25 V). The percent recovery for each analyte was determined by comparison to an internal standard~~ for each analyte~~. Standard concentrations were in the range of 7.6–152 μmol/L for acylcarnitines. Spiked samples containing different concentrations of analytes were used as daily quality control tests.

Analysis Condition

A 2.2-minute run in FIA flow at 0.070 μL/min (A: water + 0.05% formic acid, B: acetonitrile, A/B: 30%/70%). Column oven 30 °C, desolvation line 300 °C, sample injection volume 40 μL, interface temperature 500 °C, nebulizing gas 3 L/min, and drying gas 20 L/min. All data were reprocessed using Shimadzu Neonatal Software, which automatically calculates the concentration of each compound.

Statistical analysis

The data were analyzed using SPSS for Windows version 22.0 software (IBM SPSS Inc, Chicago, IL, USA). Shapiro-Wilk test was used to analyze the normal distribution. Paired sample t-test was applied using mean ± standard deviation values for normally distributed data. Wilcoxon test was performed using median and interquartile (IQR) value for non-normally data. A value of $p < 0.05$ was accepted as statistically significant.

Ethical Approval

This study was approved by the Harran University Faculty of Medicine Ethics Committee (number: HRU/20.08.07, date: 27.04.2020). Informed consent was obtained from all patients. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

The average age of patients comprising **of** 11 (44%) men and 14 (66%) women was 18.28 ± 3.98 years (12-25). Twelve (48%) of the patients were under the age of 18 and 13 (52%) were over 18 years. Of those under the age of 18, 7 were female and 5 were male. In the investigation for twenty-seven carnitine derivatives, tear levels of 15 carnitine derivatives (free carnitine and 14 acyl carnitine) could be measured. The distribution of all carnitine derivative levels before and after CXL treatment is shown in **Table 1.** Accordingly, after CXL treatment, statistically significant changes were only detected in C12 (Dodecanoil Canitine) and C14 (Myristoil Canitine) levels. A decrease was detected in both carnitine derivatives (p: 0.045, 0.038, respectively).

It was observed that there was some decrease in free carnitine levels after CXL treatment, but this decrease was not significant (p = 0.346). Among all carnitines, only C4 and C6 carnitine levels increased, but this increase was not statistically significant (p: 0.0707, 0.086, respectively), **(Figure-1), (Table-1).**

Table 1. The acylcarnitines in the tear samples of the two studied groups quantified using the LC-MS/MS method

Acylcarnitines	m/z	Formula	Status	Pre-CXL (n:) Mean ± SD	Post-CXL (n:) Mean ± SD	Fold change	p
C0 (free carnitine)	218.20>103.00	C7H15NO3	↓	14.81 ± 8.90	12.65 ± 6.21	-1.17	0.346

C2 (acetyl carnitine)	260.20>85.00	C9H17NO4	↓	1.72 ± 1.09	1.59 ± 1.20	-1.08	0.656
C3 (propionyl carnitine)	274.20>85.00	C10H19NO4	↓	1.12 ± 0.69	0.91 ± 0.60	-1.23	0.287
C4 (butyryl carnitine)	288.20>85.00	C11H21NO4	↑	0.38 ± 0.20	0.40 ± 0.19	0.95	0.707
C4DC (methylmalonyl carnitine)	374.30>85.00	C11H19NO6		Ø	Ø		
C5 (isovaleryl carnitine)	302.20>85.00	C12H23NO4	↓	1.68 ± 1.15	1.41 ± 1.35	-1.19	0.360
C5:1 (tiglyl carnitine)	300.20>85.00	C12H21NO4	↔	0.03 ± 0.02	0.03 ± 0.02	0	0.841
C5OH (isovaleryl carnitine)	318.20>85.00	C12H23NO4	↔	0.03 ± 0.01	0.03±0.02	0	0.452
C5DC (glutaryl carnitine)	388.30>85.00	C12H21NO6	↔	0.04 ± 0.02	0.04 ± 0.02	0	0.959
C6 (hexanoyl carnitine)	316.20>85.00	C13H25NO4	↑	0.06 ± 0.04	0.09 ± 0.05	0.66	0.086
C6DC (adipoyl carnitine)	344.20>85.00	C13H23NO6	↔	Ø	Ø		
C8 (octanoyl carnitine)	342.20>85.00	C15H29NO4	↓	0.02 ±0.01	0.01 ± 0.01	-2	0.151
C8:1 (octenoil carnitine)	302.20>85.00	C15H27NO4	↓	0.07 ± 0.06	0.05 ± 0.06	-1.4	0.367
C8DC (suberyl carnitine)	430.40>85.00	C15H27NO6		Ø	Ø		
C10 (decanoyl carnitine)	372.30>85.00	C17H33NO4	↔	0.01±0.01	0.01±0.008	0	0.092
C10:1 (decenoil carnitine)	370.30>85.00	C17H31NO4		Ø	Ø		
C10DC (sebacoyl carnitine)	458.40>85.00	C17H31NO6		Ø	Ø		
C12 (dodecanoyl carnitine)	400.30>85.00	C19H37NO4	↓	0.02 ± 0.01	0.01 ± 0.009	-2	0.045
C14 (myristoyl carnitine)	428.40>85.00	C21H41NO4	↓	0.02 ± 0.01	0.01 ± 0.008	-2	0.038
C14:1(tetradecenoyl carnitine)	426.40>85.00	C21H39NO4		Ø	Ø		
C14:2(tetradecadienoyl carnitine)	424.40>85.00	C21H37NO4		Ø	Ø		
C16 (palmitoyl carnitine)	456.40>85.00	C23H45NO4	↓	0.06 ± 0.04	0.04 ± 0.02	-1.5	0.457
C16:1 (hexadecenoyl carnitine)	454.40>85.00	C23H45NO4		Ø	Ø		
C18 (stearoyl carnitine)	484.40>85.00	C25H49NO4		Ø	Ø		
C18:1 (oleoyl carnitine)	482.40>85.00	C23H45NO4		Ø	Ø		
C18:2 (linoleyl carnitine)	480.40>85.00	C23H45NO4		Ø	Ø		
C18:1OH (hydroxoleoyl carnitine)	498.40>85.00	C25H49NO4		Ø	Ø		

Abbreviations: * p<0.05 and **p<0.001 values for the comparison of the variables between two groups were calculated according to the Mann-Whitney U test. (m/z: mass of main ion and product ion)

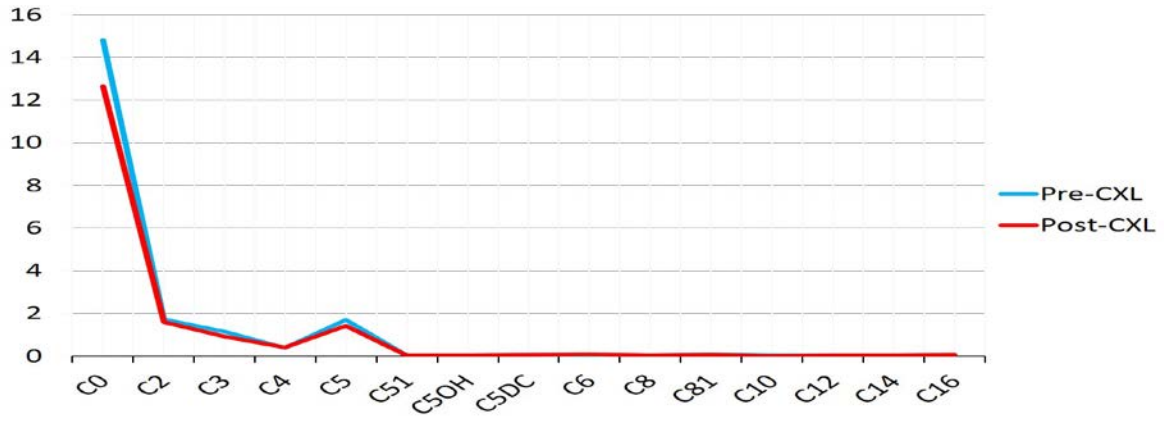

Figure 1. Tear acylcarnitine levels pre- and post- crosslinking

While the C6 level increased statistically significantly only in the group under the age of 18 (0.048 μg / ml increase, p: 0.032), it was not significant even though there was an increase in the group over the age of 18 (0.007 μg / ml increase, p: 0.691). Among the age groups, the highest difference was in carnitine derivative C6, and the least differing carnitine derivative was C51 and C5DC **(Figüre-2)**.

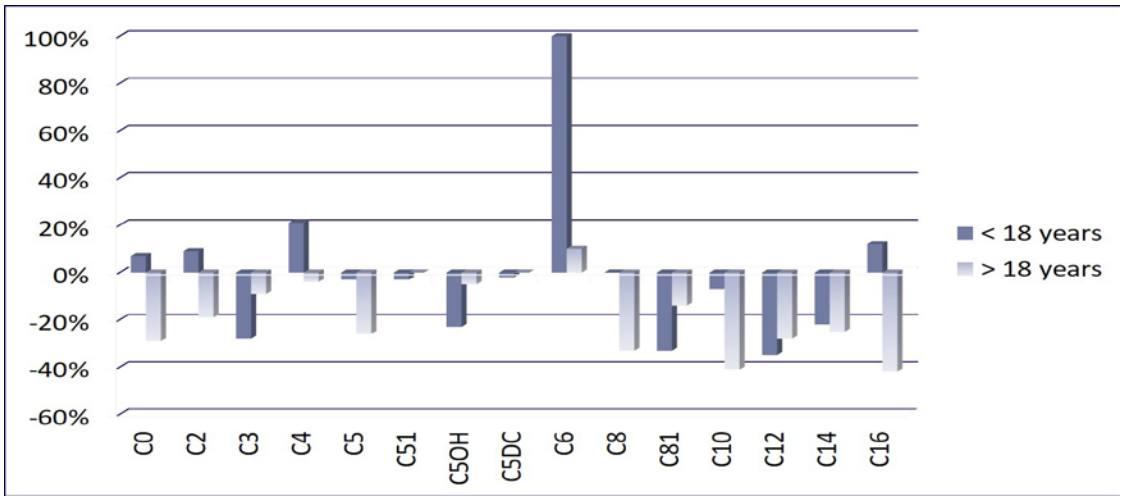

Figure 2. Distribution of the difference in tear acylcarnitine levels before and after crosslinking by age groups

Considering the overall change in carnitine derivatives, the change in male patients was greater than that of female patients **(Figure 3)**. The carnitine derivatives that differed most between the gender groups were C6 and C16, while those that differed least were C5DC and C8. C6 and C16 levels were higher in males than in females.
It was observed that a postoperative corneal scar developed in one case, which did not cause vision loss. In this case, a significant increase was observed in all carnitine derivatives except for C14 (0.01 μg/mL) and C16 (0.04 μg/mL).

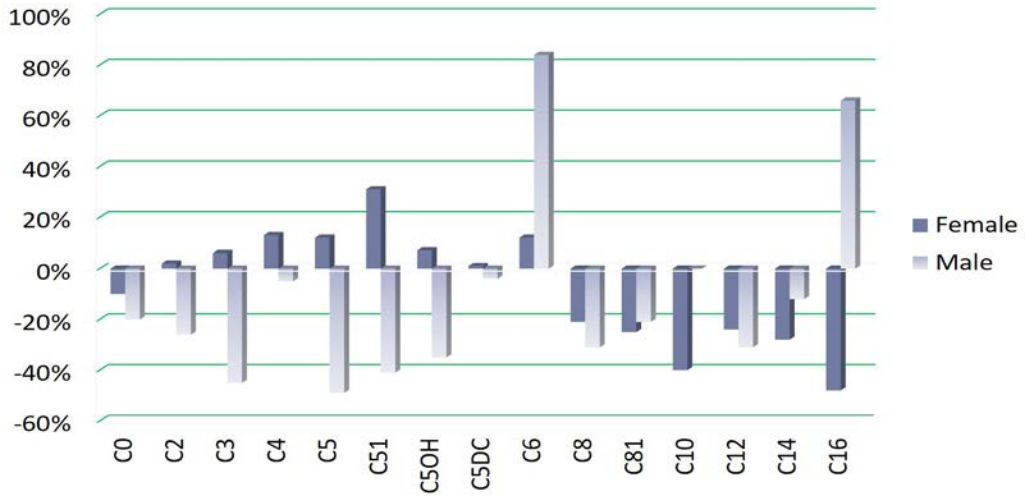

Figure 3. Distribution of difference in tear acylcarnitine levels before and after crosslinking by gender

Discussion

Fatty acids are used as an energy substrate in all tissues except the brain (14). Carnitine is an amino acid derivative that facilitates the transport of long-chain fatty acids into mitochondria and provides a substrate for oxidation and energy production. A decrease in carnitine levels in the cell is expected with inflammation and increased energy

consumption of the cell (15). Although the pathogenesis of keratoconus has not been clarified, metabolomic changes in tears have been demonstrated in pre- and post-CXL comparisons (16). In another study investigating the activity of metabolomics related to energy production in keratoconus and healthy corneas, increased carnitine synthesis activity was reported in corneas with keratoconus (17). In fact, significantly reduced carnitine levels in keratoconus corneas were detected in a study comparing keratoconus corneas to post-mortem corneas (18). The most important function of biological fluids circulating in the body is the transport of nutrients to tissues and the removal of metabolic waste. On the other hand, apart from the function of carnitine in energy metabolism, it has been reported that carnitine enhances the activity of the enzymes that scavenge free radicals in the tear, such as catalase and glutathione peroxidase (19). Also, lower GSH levels have been reported in tear samples from patients with KC (20). In the study by Snytnikova et al comparing aqueous humor in eyes with keratoconus and post-mortem normal corneas, carnitine concentrations in aqueous humor were shown to be decreased in the group with keratoconus (18). n a study investigating the relationship between tear film carnitine and dry eye, patients with dry eye disease were shown to have significantly lower carnitine levels in tear fluid compared to controls; the authors suggested using solutions containing carnitine to reduce ocular surface damage in these patients (21). As a result of active transport of ocular tissues through the cell membrane, the reduction of carnitine levels in the tear film has been shown (22,23). In addition, inflammation negatively affects carnitine metabolism in the cells. Previous studies have reported that plasma carnitine levels are reduced in inflammatory processes in particular (24). Therefore, we think that increased carnitine levels in the tear film after CXL in the current study are also compatible with these results and that CXL may be effective in suppressing possible inflammation. In asthmatic patients, whose pathophysiology is similar to keratoconus, where inflammatory mechanisms play a role, serum myristoyl carnitine and dodecanoyl carnitine were found to be significantly higher in asthmatic patients than in healthy controls (25). Similarly, in our study, a significant decrease in dodecanoyl carnitine and myristoyl carnitine levels was found secondary to the regression of inflammation after CXL treatment. In the cornea, keratocytes or fibroblasts play a central role in mediating the corneal response after injury. After injury, the keratocytes next to the wound undergo apoptosis, while those farther away from the wound transform into fibroblasts and/or myofibroblasts. At the end of these processes, scar tissue develops (26). Therefore, high carnitine concentrations in the tear film in the case with corneal scar development in this study can be explained by the increase in energy demand due to the increase in the activity of keratocytes, and an increase in carnitine transport through the tear film to compensate for this need. With a similar approach, in the study in which we previously investigated carnitine levels in pterygium tissue, where energy metabolism was accelerated due to premalignant cells and chronic inflammation, we demonstrated increased carnitine levels compared to normal conjunctival tissue (27). albis-Estrada et al, by prescribing oral nutraceutical supplements in dry-eyed patients, concluded that the tear metabolomic profile in patients with dry eye disease can be modified by appropriate oral supplements containing antioxidants and essential fatty acids (28). With this approach, we believe that it would be useful to investigate whether it would be beneficial to enhance carnitine production in order to minimize or prevent scar tissue that may develop after CXL.

Study limitations

One of them is that no tear samples were collected from the healthy population, and no comparison was made with healthy controls. Another limitation is the relatively small sample size, especially the small number of patients who developed corneal scars. A longer postoperative follow-up period could provide more robust insights into variations in carnitine levels over time.

Conclusion

The results of this study showed that the change in carnitine levels before and after CXL in KC patients may be a useful marker for monitoring inflammation and intervening in case of excessive inflammation.

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Ethical Approval: *This Study approval was obtained from the Harran University Faculty of Medicine, Ethics Committee (number: HRU/20.08.07 date: 27.04.2020). Informed consent was obtained from all patients.*

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Data Availability: *The data used to support the findings of this study are available from the corresponding author upon reques*

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Association between Hypercobalaminemia and Chronic Diseases in Outpatients: A Retrospective Case-Control Study

Ayaktan Tedavi Gören Hastalarda Hiperkobalaminemi ile Kronik Hastalıklar Arasındaki İlişki: Retrospektif Bir Vaka-Kontrol Çalışması

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Abstract

Background: Several studies have shown that high levels of Cobalamin (vitamin B12) are associated with specific diseases, such as solid cancers, chronic liver diseases, cardiovascular diseases, and others. In this study, we aimed to compare the rates the vitamin B12 in adults with and without chronic diseases.

Materials and Methods In the study, 68 (53.1%) participants with chronic disease and 60 (46.9%) participants without chronic disease were included in the study among 128 patients aged 35 and over with high vitamin B12 levels who applied to the Family Medicine Polyclinics as outpatients for a period of 1 year. Patients with vitamin B12 levels of ≥1000 pg/mL were classified as having very high levels, while those with levels between 663 and 999 pg/mL were classified as having high levels.

Results: In our study, a significant relationship was found between the presence of chronic disease and high vitamin B12 levels (p=0.017). Among chronic diseases, high levels of vitamin B12 have been found to be more significant in patients with Diabetes Mellitus (DM) (p<0.006). According to the categorization of high vitamin B12 in itself, it has been observed that vitamin B12 levels are significantly at very high levels in individuals with DM. Logistic regression analysis revealed that the risk of DM diagnosis was 0.67 times higher in those with elevated vitamin B12.

A significant relationship has been found between high levels of vitamin B12 and those with chronic diseases, especially DM.

Conclusions: It has been shown that individuals with common chronic diseases have significantly high levels of vitamin B12. We observed that very high levels of vitamin B12 are a risk factor for chronic diseases, including Type 2 DM.

Keywords: Vitamin B12, Chronic Disease, Diabetes Mellitus, Case-Control Study

ÖZ

Amaç: Çeşitli çalışmalar, kobalaminin (vitamin B12) yüksek düzeylerinin solid tümörler, kronik karaciğer hastalıkları, kardiyovasküler hastalıklar gibi bazı hastalıklarla ilişkili olduğunu göstermektedir. Bu çalışmada, kronik hastalığı olan ve olmayan yetişkin bireylerde vitamin B12 düzeylerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmaya, bir yıl boyunca Aile Hekimliği polikliniklerine başvuran ve vitamin B12 düzeyi yüksek olan 35 yaş ve üzeri 128 hasta dahil edildi. Katılımcıların 68'i (%53,1) kronik hastalığı olan, 60'ı (%46,9) ise kronik hastalığı olmayan bireylerden oluşmaktaydı. Serum vitamin B12 düzeyi ≥1000 pg/mL olanlar "çok yüksek", 663–999 pg/mL arasında olanlar ise "yüksek" olarak sınıflandırıldı.

Bulgular: Kronik hastalığı olan bireylerde vitamin B12 düzeylerinin anlamlı şekilde yüksek olduğu saptandı (p=0,017). Özellikle Diabetes Mellitus (DM) hastalarında bu ilişki daha belirgin olup, bu grupta çok yüksek vitamin B12 düzeylerine daha sık rastlandı (p<0,006). Lojistik regresyon analizine göre, yüksek vitamin B12 düzeyine sahip bireylerde DM saptanma riski 0,67 kat daha fazlaydı.

Sonuç: Yaygın kronik hastalıklara sahip bireylerde vitamin B12 düzeylerinin anlamlı derecede yüksek olduğu görülmüştür. Özellikle Tip 2 DM hastalarında çok yüksek vitamin B12 düzeylerinin bir risk faktörü olabileceği düşünülmektedir.

Anahtar Kelimeler: Vitamin B12, Kronik Hastalık, Diabetes Mellitus, Olgu-Kontrol Çalışması

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Highlights

- Final-year nursing and midwifery students face high risk of sharp object injuries during clinical practice.
- Fishbone diagram used to identify root causes: personnel, equipment, environment, and procedures. 86.7% of participants reported experiencing at least one sharp object injury.
- All identified causes were preventable, indicating potential for effective interventions.
- Study offers a novel perspective to enhance safety awareness in clinical education

Introduction

Vitamin B12 is involved in the maturation of blood cells in the body, the functions of the nervous system and DNA synthesis. High levels of vitamin B12 (Hypercobalaminemia) are a frequently encountered abnormality (1). A study conducted in Denmark in 2012 on patients not receiving vitamin B12 treatment showed that high serum vitamin B12 levels were associated with increased haptocorrin levels. The underlying causes in these patients were found to be alcoholism, liver diseases, and cancer (2). Although there are studies that have found an association between patients with chronic diseases and malignancies hospitalized in hospitals or intensive care units and high levels of vitamin B12, there is insufficient data on this issue in outpatient patients. In this study, we aimed to compare the rates of vitamin B12 elevation in adults with and without chronic diseases who were admitted to the hospital as outpatients.

Material and Methods

Study Population

Patients who applied to the Family Medicine outpatient clinic of Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between 01.06.2021 and 01.06.2022 were included.

The total number of over 35 patients who applied to Family Medicine and had their vitamin B12 levels checked is 8210. Among them, a total of 769 individuals with low levels of vitamin B12 and 6733 individuals with normal vitamin B12 levels were not included in the research. Out of the remaining 708 individuals, 558 were omitted from the research because of insufficient data, while 22 were excluded because they were utilizing vitamin B12 and folic acid-containing supplements. Consequently, a total of 128 individuals, including 85 females and 43 males, who were above the age limit of 35 and had high vitamin B12 levels, were selected to participate in the research.

Patients who applied to the Family Medicine outpatient clinic of the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between 01.06.2021 and 01.06.2022 were included. The total number of patients over the age of 35 who applied to Family Medicine and had their vitamin B12 levels checked was 8210. Among them, a total of 769 individuals with low levels of vitamin B12 and 6733 individuals with normal vitamin B12 levels were not included in the study. Out of the remaining 708 individuals, 558 were excluded due to insufficient data, while 22 were excluded because they were using vitamin B12- and folic acid-containing supplements. Consequently, a total of 128 individuals, including 85 females and 43 males, who were above the age of 35 and had high vitamin B12 levels, were selected to participate in the study.

Identification of chronic diseases

Determined International Statistical Classification of Diseases: Oath-Related Health Patients whose diagnosis was entered with one of the Problems (ICD) codes were included in the case group of the study **(Table 1).**

Vitamin B12 and other laboratory tests

Vitamin B12 was measured using Roche Cobas E801 autoanalyzer (Roche Diagnostics, Tokyo, Japan) from the examinations of patients when they were admitted as outpatients. A separate categorization was made in which individuals with vitamin B12 levels of 1000 pg/ml and above were considered very high, and individuals with vitamin B12 levels between 663 and 999 pg/ml were considered high (10,11). In addition, whole blood parameters, urea, creatinine, ALT, and AST values were also analyzed within the scope of the study.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 25.0 was used to analyze the data for Windows. Frequencies and percentages were used in categorical variables for descriptive statistics, and the Chi-square test was applied

to determine the statistical differences of the participants' characteristics. In descriptive statistics of numerical variables mean, standard deviation, median, minimum and maximum values were used. In the statistical analysis comparing vitamin B12 levels, which do not conform to a normal distribution, with demographic characteristics, the Mann-Whitney U test and Spearman correlation analysis were used. Logistic regression analysis was used to investigate the effect of vitamin B12 levels on Type 2 Diabetes Mellitus (Type 2 DM). The level of statistical significance was set at $p<0.05$.

Ethical approve

This study was conducted in accordance with the Declaration of Helsinki and institutional ethical guidelines. The study was approved by the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Number: 144/01, Date: 15.08.2022). Since this study was retrospective, informed patient consent statement was not obtained.

Results

Eighty percent of the participants were female and 20% were male. The mean age was 22.30±0.702 (Min 21-Max 24). Out of the 128 cases examined in the study, 85 (66.4%) were female and 43 (33.6%) were male. The overall median age of the patient population was 54, with women having a median age of 52 and males having a median age of 61 years. The research comprised 68 people (53.1%) with chronic condition and 60 participants (46.9%) without a chronic disease. Out of the patients with chronic illnesses, 14 (10.9%) had coronary artery disease, 51 (39.8%) had hypertension, and 41 (39.8%) had T2DM. The patient had multiple concurrent chronic conditions, including hypertension, coronary artery disease, T2DM, long-standing renal failure, rheumatoid arthritis, chronic myeloproliferative disease, liver disease, and solid tumors.

Table 1. ICD codes of chronic diseases

C81	Hodgkin's disease	E85	Amyloidosis
C83	Burkitt tumor	I10	Hypertension
C85	Non-Hodgkin's disease	I25	Atherosclerotic heart disease
C88	Waldenström macroglobulinemia	I50	Congestive heart failure
C90	Multiple myeloma	K72	Liver failure
C91	ALL, KLL	K76	Liver disease
C92	KML, AML	K77	Liver disorder
C95	Leukemias	M06	Rheumatoid arthritis
D45	Polycythemia Vera	M98	Plasma cell leukemia
D46	Myelodysplastic Syndrome	N18	Kidney failure
D47	Chronic myeloproliferative disease	N28	Kidney and ureter disorder
D75	Essential thrombocytosis	Q82	Mastocytosis
E14	Type 2 DM	R94	Abnormal disturbance of kidney function studies

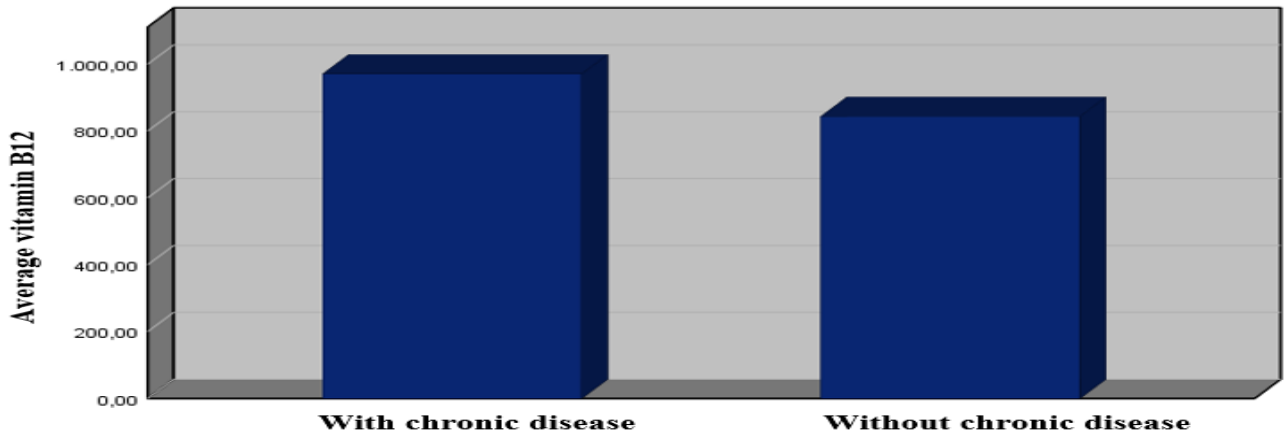

Figure 1. Evaluation of vitamin B12 according to the presence of chronic disease

The research presents the biochemical blood parameters of the individuals, which are displayed in **Table 2**.

Table 2. Biochemical blood parameters of the individuals

Parameters	Mean ± SD	Median (IQR)
Vitamin B12	910.93 ± 335.40	764.50 (664-2000)
Urea	32.14 ± 14.43	29.91 (10-130.81)
Creatinine	0.80 ± 0.24	0.75 (0.47-2.20)
AST	23.31 ± 26.27	18.70 (9.50-295.10)
ALT	19.05 ± 26.21	19.03 (5.10-382.47)
WBC	7.74 ± 2.57	7.24 (3.50-24.85)
Hb	13.82 ± 2.57	13.82 (8.20-18.10)
HCT	41.92 ± 4.45	41.48 (28.8-53.86)
MCV	86.74 ± 6.63	87.86 (63.51-103.32)
PLT	265.77 ± 71.55	263 (46-508)

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White Blood Cell, Hb: Haemoglobin, HTC: Haematocrit, MCV: Mean Cell Volume, PLT: Platelets

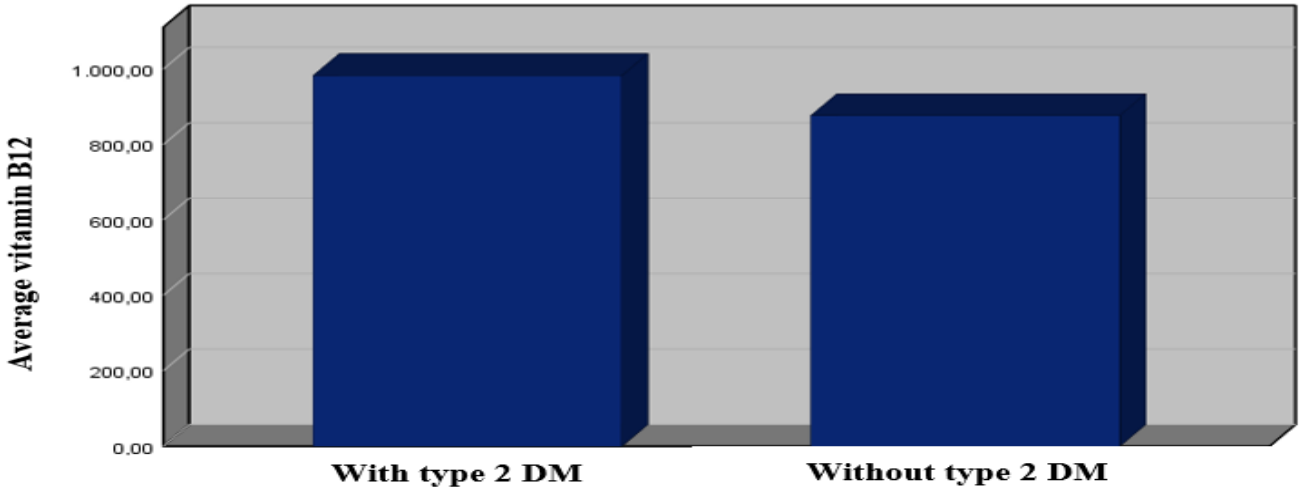

Figure 2. Evaluation of vitamin B12 according to the presence of Type 2 DM

Upon comparing vitamin B12 levels among various types of chronic illnesses, it was shown that individuals with chronic diseases had significantly higher vitamin B12 levels compared to those without chronic illnesses ($p = 0.017$). Furthermore, it was shown that individuals with T2DM had notably elevated vitamin B12 levels compared to other chronic illnesses examined according to the ICD-10 classification ($p = 0.006$).
(Table 3).

Table 3. Correlation between chronic illnesses, different kinds of diseases, and levels of vitamin B12

Vitamin B12 Level (pg / ml)	n (%)	Median (IQR)	Mean ± Sd	p
Presence of Chronic Disease	68(53.1)	823(665-2000)	970.6 ± 373.8	[a] 0.017 *
Coronary Artery Disease	14(10.9)	776(665-1842)	877.5 ± 307.6	[a] 0.781
Hypertension	51(39.8)	812(665-2000)	978.3 ± 393.8	[a] 0.190
Type 2 DM	41(32.0)	863(665-2000)	983.0 ± 337.0	[a] 0.006 *
Chronic renal failure	2(1.6)	970(946-994)	970.0 ± 33.9	[a] 0.244
Rheumatoid Arthritis	4(3.1)	832(691-1063)	854.5 ± 157.6	[a] 0.737
Chronic Myeloproliferative Diseases	2(1.6)	730(719-742)	730.5 ± 16.2	[a] 0.487
Liver Diseases	1(0.8)	843(843-843)	843	[a] 0.737
Solid Tumors	8(6.3)	825(667-2000)	1095.3 ± 535.6	[a] 0.488

Abbreviations: [a] Mann Whitney U Test * A significance threshold of $p<0.05$ was used to ascertain statistical significance

Comparison of the relationship between individuals with and without chronic diseases for other laboratory parameters except vitamin B12 in Table 4. According to a separate categorization (11,12), in which participants with vitamin B12 levels above 1000 pg/mL were considered very high, and patients with levels between 663 and 1000 pg/mL were considered high, the relationship with T2DM was evaluated. Accordingly, participants with T2DM had substantially elevated vitamin B12 levels compared to those without a history of T2DM (p=0.010). According to the results of the Cremers V test, the positive linear relationship between the two variables was low (r =0.228, p = 0.010) (Table 5).

A logistic regression analysis, using elevated levels of vitamin B12 as the reference category, revealed that individuals with high vitamin B12 levels were 2.122 times more likely to have T2DM compared to those with low vitamin B12 levels (Exp(B) = 2.122). Based on this result, the estimated probability of having T2DM among individuals with high vitamin B12 levels was approximately 67% (P = 2.122 / [1 + 2.122] ≈ 0.67). Conversely, the probability of having T2DM in individuals with low vitamin B12 levels was estimated at approximately 33% (1 – 0.67). The logistic regression model demonstrated an overall prediction accuracy of 68.0%, indicating a moderate level of model performance **(Table 6).**

Table 4. Comparison of lab parameters (without vitamin B12) by chronic disease status

Parameters	With chronic disease	Without chronic disease	p
Urea	33.8 ± 16.2	30.2 ± 11.9	[a]0.170
Creatinine	0.84 ± 0.30	0.75 ± 0.15	[a]0.170
AST	21.0 ± 11.5	25.8 ± 36.3	[a]0.430
ALT	22.2 ± 16.0	29.2 ± 48.9	[a]0.940
WBC	7.77 ± 2.11	7.70 ± 3.11	[a]0.310
Hb	13.8 ± 1.6	13.8 ± 1.8	[b]0.820
HCT	41.6 ± 0.6	42.1 ± 0.5	[b]0.500
MCV	86.3 ± 6.14	87.2 ± 6.9	[a]0.120
PLT	264.5 ± 78.2	267.0 ± 63.5	[a]0.590

Abbreviations: [a]Mann Whitney U Test [b]Independant T Test, * A significance threshold of p<0.05 was used to ascertain statistical significance, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White Blood Cell, Hb: Haemoglobin, HTC: Haematocrit, MCV: Mean Cell Volume, PLT: Platelets

Table 5. Classify Type 2 DM based on vitamin B12 levels

	Vitamin B12 (pg /ml) (n=128)			Statistical analysis		
	Vitamin B12>1000, n (%)	**VitaminB12<1000, n (%)**	**Total, n (%)**	**x^2**	**SD**	**p**
Type 2 DM	15(36.6)	26(63.4)	41(100)	6.679	one	**0.010***

Abbreviations: * Continuity Correction, Chi-square χ2: Chi-square, A significance threshold of p<0.05 was used to ascertain statistical significance

Table 6. Regression between vitamin B12 levels and Type 2 DM

	B.	sh	Wald	sd.	p	Exp B)	95% for Exp (B) CI	
							Low	High
Vitamin B12 (continuous variable)	0.001	0.001	0.565	one	0.452	1.001	0.999	1.003
Vitamin B12 (categorized)	-1.576	0.769	4.197	one	0.040*	0.207	0.046	0.934

Abbreviations: Univariant logistic regression analysis *p<0.05 was considered significant. CI: confidence interval

Nagelkarke R^2 =0.074, Omnibus Chi-square=6.938, df:2, p=0.000, Hosmer and Lemeshow >0.05

Based on the normal distribution of vitamin B12 levels, Spearman correlation analysis revealed a statistically significant but weak positive correlation between vitamin B12 levels and both age (p = 0.041) and AST levels (p = 0.006). As age (r = +0.181) and AST (r = +0.243) increased, a significant increase in vitamin B12 levels was observed. No significant correlation was found between vitamin B12 levels and other blood parameters (**Table 7**)

Table 7. Evaluation of the relationship between vitamin B12 levels and Age and AST value

	Vitamin B12 levels		
	n	**r**	**p**
Age	128	0.181	0.041*
AST	128	0.243	0.006*

Abbreviations: Spearman correlation analysis *p<0.05 was considered significant.

Discussion

We found that vitamin B12 levels in individuals with chronic illnesses were significantly higher compared to those without chronic illnesses. Especially those with Type 2 Diabetes Mellitus (T2DM), we found that the number of individuals with vitamin B12 levels above 1000 pg/ml were significantly high. Additionally, we found a weak positive correlation between age and vitamin B12 levels.

In hypercobalaminaemia, the patient's treatment with pharmacological doses of vitamin B12 explains this condition, as the treatment will lead to an increase in TC saturation (4).

While a low vitamin B12 level does not directly indicate deficiency, abnormally high levels serve as a warning that underlying serious pathologies should be ruled out. Most of the causes of hypercobalaminemia are related to quantitative anomalies involving transcobalamin (1). It is thought that pathogenic causes include increased concentrations of circulating cobalamin-binding proteins, TC and HC, either one or both (4). There are several pathophysiological mechanisms in hypercobalaminaemia:

- A direct increase in plasma vitamin B12 due to excessive intake or administration
- A direct increase in plasma vitamin B12 released from body stores
- An increase caused by overproduction of TC or decreased clearance
- An affinity deficiency of TC for vitamin B12

Prolonged parenteral intake of vitamin B12 can lead to the development of anti-TC-II autoantibodies, which may result in decreased clearance of TC-II. This induced autoimmunization has been observed in 30% of a group of Danish patients receiving treatment for pernicious anemia. In cases of liver cancer, the mechanisms causing hypercobalaminemia include a decrease in the hepatic clearance of the HC-vitamin B12 complex and an increase in plasma levels of TC due to extensive hepatocyte destruction. The decrease in hepatic clearance is thought to be associated with poor hepatic vascularization and a reduction in the number of HC receptors on the surface of cancerous hepatocytes. In other solid tumors, the cause of hypercobalaminemia is primarily thought to be related to the tumor's excessive synthesis of TC or an increase in HCs due to the stimulation of leukocytosis. In myeloid proliferations, hypercobalaminemia is primarily associated with the release of HCs by tumor granulocytes and their precursors. Since the liver is involved in vitamin B12 metabolism, acute and chronic liver diseases also play a role in high serum vitamin B12 levels. In acute hepatitis, it is thought that excessive release of cobalamin by the liver and a decrease in hepatic synthesis of TC-II, which is necessary for the binding of vitamin B12 to tissues, occur. In patients with cirrhosis, the main mechanisms involve a decrease in the hepatic uptake of vitamin B12 and HC-vitamin B12 complex at the tissue and cellular levels, which has been characterized by biopsy. In a study conducted on alcoholic liver diseases, an increase in the plasma levels of TC-I and TC-III was observed, which binds to vitamin B12 and prevents the eventual elimination of plasma vitamin B12. The same study showed that a decrease in TC-II levels led to impairments in the transfer of vitamin B12 to tissues. It is thought that the TC-II receptor, which is abundantly found in the kidney, may impair the cellular uptake of vitamin B12 (1). In a study conducted by Arendt et al., it was found that as age increases, there are more patients with high blood levels of vitamin B12 (2). In the study conducted by Kansal et al., it was found that individuals aged 65 and above had higher vitamin B12 levels compared to those aged 18-64, and that vitamin B12 levels showed a positive correlation with age (5). Research has been conducted on different patient groups to use vitamin B12 levels as a prognostic marker of mortality (6-8). Especially in patients with HCC (Hepatocellular Carcinoma) or hepatic metastasis, hypercobalaminemia has been found to have a positive association with the risk of mortality. These studies have led to the introduction of the BCI (Vitamin B12 to CRP levels ratio index) as a mortality indicator, but its use in clinical practice has not yet become widespread (4-9-10). "In the study conducted by Couderc et al. on elderly cancer patients, a significant relationship was found between BCI and mortality (11). In similar studies, it has been found that patients with a BCI level above 40,000 have a shorter survival time (12-13). As a result of all these studies, more research on vitamin B12 and BCI is needed to explore new prognostic markers in diseases and aid in early diagnosis, especially in malignancies. Comprehensive studies are required.

Hypercobalaminemia has been associated with many causes, primarily serious and life-threatening diseases. Available data and studies have raised numerous questions and prompted further research. Investigating vitamin B12 metabolism in certain diseases, treating hypercobalaminemia in clinical practice, and measuring TC and/or HC in laboratory tests highlight the importance of early intervention in these conditions (4). As a result of the study conducted by Anwaar et al., higher vitamin B12 levels were found in diabetics compared to individuals with abnormal and normal glucose homeostasis (14). Another study investigated the relationship between glycemic fluctuations and vitamin B12 levels in patients with Type 2 DM, finding that individuals with more frequent glycemic fluctuations had higher vitamin B12 levels (15). Meta- analyses have found that the prevalence of vitamin B12 deficiency in patients with Type 2 DM using metformin is higher compared to those who do not use it. Additionally, the daily dose and duration of metformin use play a role in this association (16-17). Similarly, in the study by Khattab et al., a positive correlation was found between long-term metformin use and vitamin B12 deficiency (18). While previous studies have shown vitamin B12 deficiency due to metformin use in DM patients, our study and several supporting studies reveal the opposite findings, indicating that more research is needed in this area. Although the exact mechanism by which Type 2 DM causes elevated vitamin B12 levels is not yet clearly understood, we hypothesize that this may result from impaired liver or kidney functions associated with the disease.

Study limitations

There are some limitations in our study. It is a single-center, retrospective study conducted over a certain period and includes a small number of patients. Although there were a variety of chronic diseases in our study, the number of patients analyzed in each category was insufficient. When the additions of the study to the literature are considered, it is seen that the relationship between vitamin B12 levels and chronic diseases is complicated by several factors, as the patients' dietary habits, lifestyles, and whether they receive additional nutritional support are based on subjective responses, which may act as confounding factors affecting vitamin B12 levels. It has been observed in the literature that there is a clear need for large-scale, multicenter, randomized controlled cohort studies on this subject.

Conclusion

When considering the contributions of the study to the literature, it should not be overlooked that there may not be a direct relationship between vitamin B12 levels and chronic diseases; given that diet, medications, supplements, and the metabolic effects of aging are confounding factors, there is a natural difficulty in establishing this relationship. In addition to the adverse effect of metformin, the first choice in the treatment of Type 2 DM, on vitamin B12 levels, we believe it is worth investigating whether there are mechanisms in the pathogenesis of diabetes itself that may hinder the accumulation and metabolism of vitamin B12.

It has been shown that individuals with common chronic diseases have significantly high levels of vitamin B12. We observed that very high levels of vitamin B12 are a risk factor for chronic diseases, including Type 2 DM. There is a need for mechanism-focused cohorts to clearly establish the relationship between chronic diseases and vitamin B12 levels.

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Ethical Approval: *This Study approval was obtained from the Health Sciences University Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Number: 144/01, Date: 15.08. 2022). Since this study was retrospective, informed patient consent statement was not collected.*

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Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research. authorship and/or publication of this article.*

Data Availability: *The data used to support the findings of this study are available from the corresponding author upon reques*

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Retrospective Analysis of Cardiac Arrest Cases Admitted to A General Intensive Care Unit

Genel Yoğun Bakim Ünitesine Kabul Edilen Kardiyak Arrest Olgularinin Geriye Dönük Değerlendirilmesi

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Abstract

Background: Cardiac arrest(CA) is the sudden loss of heart function and is one of the leading causes of death worldwide. After successful cardiopulmonary resuscitation (CPR), patients are monitored in the intensive care unit with a diagnosis of post-cardiac arrest syndrome. To date, many clinical and laboratory parameters have been used to predict outcomes. In this study, a retrospective analysis was performed by reviewing the clinical and laboratory parameters of patients admitted to the general intensive care unit within the last three years.

Material and Methods: Data from patients admitted to the intensive care unit between June 2016 and June 2019 due to CA were reviewed retrospectively. Independent effects were analyzed using linear and binary logistic regression.

Results: Increasing age and longer durations of CPR were associated with higher mortality rates, while mortality was lower among patients who received therapeutic hypothermia. Blood urea nitrogen (BUN) and creatinine levels were higher in patients who died. Higher mean arterial pressure (MAP) was associated with longer hospital stays. In patients with elevated lactate and creatinine levels and prolonged CPR duration, the length of hospital stay was shorter. No significant relationship was observed between blood gas parameters and mortality. None of the evaluated factors independently affected the length of hospital stay or mortality.

Conclusions: According to the data from our study, these factors alone were insufficient to predict patient prognosis.

Keywords: Cardiac arrest, cardiopulmonary resuscitation, post-cardiac arrest syndrome, hypothermia treatment, prognosis.

ÖZ

Amaç: Kardiyak arrest (KA), kalp fonksiyonunun ani kaybı olup dünya genelinde önde gelen ölüm nedenlerinden biridir. Kardiyopulmoner resüsitasyonun (KPR) başarılı bir şekilde uygulanmasının ardından hastalar, kardiyak arrest sonrası sendrom tanısıyla yoğun bakım ünitesinde izlenmektedir.

Bugüne kadar sonuçları tahmin etmek için birçok klinik ve laboratuvar parametresi kullanıldı.

Bu çalışmada son üç yıl içerisinde genel yoğun bakım ünitesine yatırılan hastaların klinik ve laboratuvar parametreleri incelenerek retrospektif bir analiz yapıldı.

Gereç ve Yöntem: Haziran 2016 ile Haziran 2019 tarihleri arasında KA nedeniyle yoğun bakım ünitesine kabul edilen hastaların verileri retrospektif olarak değerlendirilmiştir. Bağımsız etkenler linear ve binary lojistik regresyon kullanılarak analiz edildi.

Bulgular: Artan yaş ve uzayan kardiyopulmoner resüsitasyon süresi, daha yüksek mortalite oranları ile ilişkili bulunmuştur. Öte yandan, terapötik hipotermi uygulanan hastalarda mortalite oranı daha düşük saptanmıştır. Kan üre azotu (BUN) ve kreatinin düzeyleri, yaşamını kaybeden hastalarda daha yüksek bulunmuştur. Ortalama arteriyel basınç (OAB) değerindeki artış, hastanede kalış süresinin uzamasıyla ilişkili bulunmuştur. Laktat ve kreatinin düzeyleri yüksek olan ve KPR süresi uzun olan hastalarda ise hastanede kalış süresi daha kısa saptanmıştır. Kan gazı parametreleri ile mortalite arasında anlamlı bir ilişki gözlenmemiştir. Değerlendirilen faktörlerin hiçbiri hastanede kalış süresini veya mortaliteyi bağımsız olarak etkilemedi

Sonuç: Çalışmamızın verilerine göre bu faktörlerin tek başına hasta prognozunu öngörmede yeterli olmadığı görüldü.

Anahtar kelimeler: Kardiyak arrest, kardiyopulmoner resüsitasyon, post kardiyak arrest sendromu, hipotermi tedavisi, prognoz.

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Highlights

- Cardiac arrest remains one of the leading causes of death worldwide, and successfully resuscitated patients require intensive care monitoring.
- This study evaluated the impact of clinical findings on the prognosis of patients admitted after cardiac arrest.
- No single clinical or laboratory factor was sufficient to independently predict prognosis.

Introduction

Cardiac arrest (CA) is defined as the abrupt cessation of effective cardiac activity. In the absence of immediate cardiopulmonary resuscitation (CPR), it invariably results in death. CPR involves the restoration of circulation through chest compressions and the maintenance of adequate oxygenation. Although CA may result from various etiologies, it most commonly arises from cardiac causes (1). The primary objective of CPR is to achieve return of spontaneous circulation (ROSC) and ultimately discharge patients without neurological impairment. Following successful CPR, patients are monitored in the intensive care unit under the diagnosis of post-cardiac arrest syndrome (2). Advances in science and technology have significantly improved CPR outcomes. The American Heart Association (AHA) regularly updates its basic and advanced life support algorithms, and these guidelines are implemented globally (3). Evidence suggests that the use of therapeutic hypothermia following CPR enhances survival rates and improves neurological outcomes (4). Enhancing the effectiveness of CPR requires prompt identification and management of the underlying causes of CA. Moreover, assessing patients' demographic characteristics, vital signs, and laboratory parameters is essential for optimizing CPR success.

To date, many clinical and laboratory parameters have been used to predict outcomes in patients with CA. In this study, a retrospective analysis was performed by reviewing the clinical and laboratory parameters of patients admitted to the general intensive care unit within the last three years.

Material and Methods

Study design

The data of patients admitted to the 3rd-level General Intensive Care Unit at Harran University Research and Application Hospital between June 2016 and June 2019 due to CA were retrospectively reviewed using the hospital information management system**.** The age, CPR duration, mean arterial pressure (MAP), Glasgow Coma Scale (GCS) score, fasting blood glucose, hemoglobin (Hgb) level, white blood cell (WBC), blood urea nitrogen (BUN), creatinine, pH, partial pressure of carbon dioxide (PaCO2), arterial oxygen saturation (SpO2), and lactate values were recorded and evaluated. All patients who underwent CPR and were admitted to the intensive care unit were included in the study. Patients younger than 18 years were excluded from the study.

Statistical analysis

Data were analyzed using SPSS for Windows version 23.0. Descriptive statistics for continuous variables were presented as median ± standard deviation, categorical variables were expressed as numbers and percentages. The normal distribution of continuous variables was determined using the Kolmogorov-Smirnov test, skewness, and kurtosis tests. Student's t-test was used to compare continuous variables between groups with and without hypothermia therapy, as the data were normally distributed**.** The Mann-Whitney U test was used for comparing the means between mortality groups, as the data did not follow a normal distribution. Categorical variables were compared using the Chi-square test. The correlation between continuous variables was evaluated using Pearson's correlation coefficient (Rho). A $p<0.05$ was considered statistically significant. The independent effects of factors that could affect the duration of hospitalization and mortality were tested using linear and binary logistic regression analyses.

Ethical Approval

This study approval was obtained from the Harran University Faculty of Medicine, Ethics Committee (number: 20.12.28. date: 29.06.2020. The data of both groups was retrospectively recorded and analyzed in the hospital automation system. This study was conducted retrospectively. Therefore, no consent form was obtained. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

Of the 120 patients initially included in the study, 20 patients who experienced in-hospital CA and 4 patients referred to another facility whose outcomes could not be evaluated were excluded. Statistical analyses were therefore performed on 96 patients. The mean age of the patients was 60.5 years. The number of male and female patients was equal (48 each). The findings of the patients at the time of admission to the intensive care unit are presented in **Table 1**. The mean admission time was 7.6 minutes, GCS score was 3.9, MAP was 72.5 mmHg, CPR duration was 23.4 minutes, and the length of stay was 16.9 days **(Table 1).**

Table 1. Admission findings of patients

Parameter	Mean	Standard Deviation
Admission time* (minutes)	7.6	8
Glasgow Coma Scale score	3.9	1
Mean arterial pressure	72.5	21.3
CPR duration (minutes)	23.4	15.9
Length of stay (days)	16.9	24.9

Abbreviations: The time interval between cardiac arrest and cardiopulmonary resuscitation initiation

In patients who did not survive, the mean age was higher (p<0.001). Additionally, CPR duration was longer in patients who died (p=0.043). As MAP increased, the length of stay also increased. Patients with prolonged CPR had a shorter length of hospital stay **(Table 2).**

Table 2. Comparison of age, admission time, GCS score, MAP, and other relevant parameters between survivors and non-survivors

Variables	Death none (n=11)	Death yes (n=85)	p
Age (years)	31.4 ± 17.4	64.3 ± 16.9	<0.001
Admission time (minutes)	6.3 ± 5.8	7.9 ± 8.4	0.765
GCS score	4.1 ± 0.8	3.8 ± 1.1	0.195
MAP	81.5 ± 11.2	71.4 ± 22.1	0.145
CPR duration (minutes)	15.9 ±11.8	24.4 ± 16.1	0.043
Length of stay (days)	17.2 ± 15.7	16.9 ± 25.9	0.138

Abbreviations: *Mann-Whitney-U test

No correlation was found between age, admission time, or GCS and the length of hospitalization. However, MAP showed a moderate positive correlation with length of hospital stay (p=0.002, r=0.311). As MAP values increased, the length of hospital stay also rose. Conversely, CPR duration exhibited a weak negative correlation with length of hospital stay (p=0.014, r=-0.252), indicating that longer CPR times were associated with shorter hospital stays. **(Table 3)**

Table 3. Correlation Analysis of Length of Hospital Stay According to Patients' Age, Admission Time, GCS, MAP, CPR Duration, lactate and creatinine level.

Variables	r*	p
Age (years)	-0.076	0.464
Admission time (minutes)	0.120	0.375
GCS score	0.112	0.276
MAP	0.311	0.002
CPR duration (minutes)	-0.252	0,014
Lactate (mg/dL)	-0,214	0.039
Creatinine (mg/dL)	-0,204	0.048

Abbreviations: *Pearson Rho Correlation; r=correlation coefficient

BUN and creatinine levels were higher in patients who died (p <0.001 and 0.007, respectively), respectively). As lactate and creatinine levels increased, the length of hospital stay decreased **(Table4).**

Table 4. Comparison of survivors and non-survivors according to fasting blood glucose, Hgb, WBC, BUN, and creatinine values

Variables	Death None (n=11)	Death Yes (n=85)	p
Glucose (mg/dL)	258.6±176.8	266.9±148.6	0.609
Hgb (mg/dL)	13.8±2.7	12.4±2.6	0.122
WBC (x10^3/μL)	24.4±9.2	20.1±10	0.106
BUN (mg/dL)	29.3±15	70±51.6	<0.001
Creatinine (mg/dL)	1.01±0.44	1.99±1.94	0.007

Abbreviations: *Mann-Whitney-U test

Table 5. Effect of Hypothermia on Mortality in Cardiac Arrest Patients

Variables	Death (None, %)	Died (Yes, %)	p
All patients	11 (11.5)	85 (88.5)	
Hypothermia **No**	1 (1.5)	64 (98.5)	<0.001
Yes	10 (32.3)	21 (67.7)	

Abbreviations: *Chi-square test

Mortality rate was lower in patients who received hypothermia treatment (p<0.001) **(Table 5).**
When we look at the independent effects of the factors that may affect the mortality rate, no factor was found to have an independent effect. Similarly, no factor independently affected the length of hospital stay **(Table 6)**.

Table 6. Independent effects of all factors on death

Variables	B	p	Exp(B)
Hypothermia	5.119	1.000	167.167
Age (years)	0.92	0.998	2.509
Admission time (minutes)	3.101	0.998	22.211
GCS	7.245	1.000	1400.504
MAP	-0.839	0.998	0.432
CPR duration (min)	1.872	0.997	6.502
pH	-164.962	0.998	0
SpO2 (%)	3.873	0.996	48.092
PaCO2 (mmHg)	-0.104	1.000	0.901
Lactate (mg/dL)	-0.856	1.000	0.425
Glucose (mg/dL)	0.036	0.999	1.036
Hgb (mg/dL)	-4.984	0.998	0.007
WBC (x10^3/μL)	-1.854	0.998	0.157
BUN (mg/dL)	0.622	0.998	1.862
Creatinine (mg/dL)	-7.967	0.999	0
Length of stay (days)	0.686	0.997	1.986
Constant	861.698	0.999	.

Abbreviations: Exp(B): estimated probability ratio, (B): coefficient

Discussion

In this study, we conducted a retrospective analysis to evaluate the potential prognostic value of several clinical and laboratory parameters in patients who experienced CA. These parameters included age, duration of CPR, MAP, GCS score, fasting blood glucose, Hgb level, WBC count, BUN, creatinine, pH, $PaCO_2$, SpO_2, lactate levels, and the application of therapeutic hypothermia.
Our principal findings indicated that none of the evaluated variables demonstrated an independent effect on either the length of hospital stay or mortality when analyzed individually. Several factors may account for this outcome, including the limited sample size and the observation that patients who received therapeutic hypothermia tended to

be younger and exhibited lower BUN and creatinine levels. These imbalances may have introduced statistical confounding, limiting the ability to identify a singular factor responsible for improved survival outcomes.

In all studies, age has been shown to be the most important prognostic factor in patients in whom spontaneous circulation was achieved after CA. It is known that the mortality rate and the risk of permanent neurological damage after CPR are higher for older individuals. A meta-analysis examining studies on this topic found that the average age of CA patients ranged from 60 to 75 years (6). In our study, a total of 96 patients were included, of whom 48 were men and 48 were women, with an average age of 60.5 years. Of these patients, 85 died after treatment, and 11 were discharged. Consistent with previous studies, we found that the average age of patients who died was 64.3 years, while the average age of survivors was 31.4 years. Therefore, similar to the literature, we found that age was a significant prognostic factor in our cohort**.**

CPR duration is also known to significantly affect the prognosis of these patients. Studies have shown that early defibrillation is the most important factor for post-CA survival (7). As the duration of CPR increases, the chance of survival decreases. One study reported that each 1-minute delay in defibrillation decreases the survival rate by 10-12% (8). While some publications state that prolonged CPR does not make a significant difference in terms of anoxic brain damage (9), a 2022 study on 8,727 patients found that shorter CPR duration significantly improved 30-day and 1-year survival rates, and that shorter durations were associated with lower rates of anoxic brain injury (10). In our study, the average CPR duration was 15.9 minutes in discharged patients, compared to 24.4 minutes in those who died. Patients who died had longer CPR durations ($p=0.043$). Additionally, as CPR duration increased, the length of hospitalization decreased. These results were consistent with the literature.

Many studies have found that systolic blood pressure below 90 mmHg in patients who survived CA is associated with poor recovery and higher mortality (11). Another study found that patients with a MAP above 100 mmHg for 2 hours after ROSC were more likely to have better neurological recovery upon discharge (12). Although many studies have shown that MAP is important in post-CA care, some studies have not found definitive evidence of its benefit or the ideal threshold for maintaining MAP. Furthermore, the effects of medications such as adrenaline during CPR and sedation during follow-up make it difficult to draw definitive conclusions about blood pressure management. Current guidelines do not offer a recommendation on target blood pressure in CA resulting from acute myocardial infarction (13). In our study, although no statistically significant difference was found in terms of mortality, there was a moderate correlation between MAP and length of hospitalization ($p=0.002$, $r=0.311$). As MAP increased, the length of stay also increased. The average MAP was 81.5 mmHg in survivors and 71.4 mmHg in those who died.

Low GCS scores in patients examined after CA have been shown to negatively impact mortality (14). In a study by Schefold et al., patients with higher GCS scores who underwent hypothermia therapy after CA were discharged with better neurological outcomes (15). In our study, we examined the GCS scores of patients at the time of admission to the emergency department after CA. However, in our study, the average GCS scores for survivors and those who died were 4.1 and 3.8, respectively, which did not align with the literature. The GCS score was similar in both patient groups, and no significant effect on mortality or length of stay was observed.

Fasting blood glucose levels are a controversial parameter in this context. Some studies suggest that high blood glucose levels do not increase mortality after CA, while others have found an association between elevated blood glucose levels and more severe neurological dysfunction and mortality (16). In our study, the average glucose levels for survivors and those who died were 258.6 mg/dL and 266.9 mg/dL, respectively. We found no significant effect of glucose levels on mortality or length of stay.

Hgb levels were also examined in our study. The distribution of oxygen throughout the body depends on both cardiac output and arterial oxygen concentration, which is directly affected by Hgb concentration. Although it seems theoretically reasonable to increase the amount of oxygen reaching tissues by increasing Hgb levels, studies have shown that initial transfusions do not reduce mortality in patients who survived CA (17). Some studies have shown that low Hgb levels worsen the prognosis in post-CA patients (18). A study conducted in 2011 found that higher Hgb levels at the time of hospital admission were associated with better neurological outcomes (19). The number of WBC was another parameter we evaluated in the hemogram analysis. Although an increase in WBC is known to have a negative prognostic effect on cardiac diseases, its usefulness in predicting the prognosis of post-CA patients has not been clearly established (20). Although some studies have shown a relationship between WBC levels and mortality (21), others have found the opposite (22). There are studies indicating that an increase in WBC count is associated with increased infectious complications in post-cardiac arrest patients (23). Our study found that the average Hgb levels for survivors and those who died were 13.8 and 12.4 g/dL, respectively, while the average

WBC levels were 24.4 $\times 10^3/\mu L$ and 20.1 $\times 10^3/\mu L$, respectively. Hgb and WBC levels did not have a significant effect on mortality or length of stay.

The level of BUN and kidney function are mentioned in many studies as factors that can be used to predict the prognosis of patients after CA (24). However, there are studies that suggest the relationship is unclear (25). Some studies have found a significant association between elevated BUN levels and increased mortality (26). Similarly, elevated creatinine levels have been shown to affect the prognosis of patients who survived CA (17). A study found that low creatinine levels reduced mortality (27). In a large cohort study conducted by Lemiale et al., elevated creatinine levels were found to increase mortality (28). In our study, the average BUN levels were 70 mg/dL in patients who died and 29.3 mg/dL in those who survived. Although no correlation was found between BUN levels and length of stay, creatinine levels showed a weak negative correlation with length of stay ($p=0.048$, $r=-0.204$). When mortality was evaluated, BUN and creatinine levels were higher in patients who died (p values <0.001 and 0.007).

Some studies suggest that certain parameters evaluated in arterial blood gas analyses can help predict the prognosis of patients after CA. pH levels are believed to be useful in prognosis prediction (29). A study found that low pH levels increased mortality (30). According to a study by Momiyama et al., higher pH levels in patients who survived CA were associated with better outcomes (31). PaCO2 is an important regulator of cerebral blood flow. Dysregulation of PaCO2 can alter cerebral blood flow, leading to worse clinical outcomes after cerebral injury (32). Some studies suggest that PaCO2 can be used to predict the prognosis of patients after CA (29). A review has shown that both hypocapnia and hypercapnia are indicators of poor prognosis in brain injury (32). SpO_2 is also considered a potential marker for this purpose. Studies suggest that low SpO_2 is associated with poor neurological outcomes (33). Not only hypoxia but also hyperoxia is harmful to the body. Research indicates that hyperoxia, by causing reperfusion injury, is linked to poor neurological outcomes. Therefore, it is recommended to avoid both hypoxia and hyperoxia in post-cardiac arrest patients (34). In a study investigating the prognosis of patients who experienced CA, higher mortality was observed in patients with low PO2 levels. However, when assessed alongside other criteria, it was found that PO2 alone is not a reliable marker for determining prognosis (30).

Another parameter evaluated in blood gas is lactate. An increase in lactate clearance is associated with reduced mortality in patients with trauma, sepsis, and burns. Effective early lactate clearance has also been found to be associated with reduced mortality in patients who survived CA (35). In another study, high lactate level was found to be associated with high mortality in patients examined after CA (30). A meta-analysis found that lower lactate levels were associated with lower mortality (27). However, some studies have shown that lactate levels are not helpful in prognosis prediction (36). In a study investigating the effects of elevated lactate levels on poor prognosis, it was suggested that higher lactate levels were associated with longer CPR times, and thus, longer hypoxic periods and more severe ischemia, leading to worse prognosis (30). The effect of blood gas values on mortality in our study was not consistent with the literature. The average pH in patients who died was 7.16, compared to 7.25 in survivors. The average SpO_2 values were 93% in patients who died and 95.5% in those who survived. The average PaCO2 values were 41.6 mmHg in patients who died and 37.4 mmHg in those who survived. The average lactate levels were 7.7 mg/dL in patients who died and 5.4 mg/dL in those who survived. Blood gas parameters were not found to be associated with mortality. However, lactate levels showed a weak negative correlation with the length of stay ($p=0.039$, $r=-0.214$). As lactate levels increased, the length of stay decreased.

Studies have shown that post-cardiac arrest mortality is lower in patients treated with hypothermia therapy (37). In a study conducted by Castrejón et al., hypothermia was found to improve the prognosis of anoxic encephalopathy (38). Although numerous studies demonstrate the benefits of hypothermia therapy, recent research has emphasized the need to focus on normothermia rather than hypothermia. A study conducted in 2021 involving 1,900 patients revealed no significant difference in six-month survival between hypothermia and normothermia (39). Similarly, a meta-analysis published by Shersta et al. in 2022 concluded that hypothermia therapy targeting 32–34 °C provided no additional benefit over normothermia in terms of mortality and neurological damage (40).

In our study, therapeutic hypothermia was applied to 31 patients. Of the 11 patients discharged, 10 had received hypothermia therapy. Although the length of hospital stay for patients receiving hypothermia therapy was similar ($p=0.133$), their mortality rate was significantly lower ($p<0.001$).

Numerous studies have proposed that various clinical and laboratory parameters may serve as predictors of prognosis in patients who are monitored following CA. We believe that early identification and evaluation of such criteria may contribute to the recognition of prognostic factors associated with mortality and morbidity. The parameters assessed in our study may provide clinical guidance in the management and follow-up of patients who

achieve ROSC after CA. However, these variables do not offer definitive prognostic conclusions regarding long-term outcomes or overall patient well-being.

Study limitations

This study has several limitations. Primarily, it is a single-center and retrospective study, which inherently restricts the generalizability of the findings. Additionally, the relatively small sample size constitutes another limitation. Due to the retrospective design, some patient data were incomplete, resulting in the exclusion of certain cases from full evaluation.

Conclusion

In our study, when examining the independent effects of factors that could impact the length of hospital stay and mortality rate, it was found that no factor had an independent effect on either the length of stay or the mortality rate. Possible reasons for this include the insufficient number of patients and the fact that the patients who received therapeutic hypothermia were younger, with lower BUN and creatinine levels, which makes it statistically difficult to determine the exact factor that affects mortality. Additionally, due to the inadequacy of records, the time of patients' arrival at the emergency department and its impact on mortality could not be evaluated.

The post-ROSC management of CA patients in the intensive care unit represents a highly complex process, shaped by multiple interacting factors. To gain a clearer understanding of prognostic determinants and optimize patient outcomes, further large-scale, long-term, and multicenter studies are warranted.

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Original Article

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Ocular Findings and Fundus Fluorescein Angiography Characteristics in Ocular Behçet's Disease

Oküler Behçet Hastalığında Oküler Bulgular ve Fundus Florescein Anjiyografi Özellikleri

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Abstract

Background: To evaluate ocular findings and the characteristics of fundus fluorescein angiography (FFA) in ocular Behçet's disease (OBD).

Material and Methods: A retrospective study was conducted on 104 patients (208 eyes) with OBD who were seen in our ophthalmology clinic between 1996 and 2006. The diagnosis of all patients was made according to the criteria of the International Study Group for Behçet's Disease. All patients underwent FFA. Information on the patients' gender, age, disease duration, ocular findings, FFA findings, ocular complications, and visual acuity were collected.

Results: The mean age of the patients included in the study was 32.54±9.45 (19-48) years. Of the total cases, 57 (54.8%) were male and 47 (45.2%) were female. Ocular involvement was bilateral in 73.1% and unilateral in 26.9% of the cases. The most common ocular finding was panuveitis, observed in 54.4% of the cases. The most frequent FFA finding was optic disc leakage, observed in 81.1% of the cases. The rate of anterior uveitis was 12.7%, while the rate of posterior uveitis was 32%. The proportion of eyes with a visual acuity of 0.5 or higher was 67.2%, those with a visual acuity between 0.5 and 0.1 were 21.1%, and those with a visual acuity of 0.1 or lower were 11.6%.

Conclusions: In OBD, the most frequent ocular finding is panuveitis, and the most common FFA finding is leakage from the optic disc. FFA plays a significant role in the diagnosis and follow-up of retinal complications in OBD.

Keywords: Fundus fluorescein angiography, Ocular Behçet's Disease, Uveitis.

ÖZ

Amaç: Oküler Behçet Hastalığında (OBH) göz bulgularını ve fundus floresein anjiyografinin (FFA) özelliklerini değerlendirmek.

Gereç ve Yöntem: 1996-2006 yılları arasında göz kliniğimizde OBD tanısıyla izlenen 104 hasta (208 göz) üzerinde retrospektif bir çalışma yürütüldü. Tüm hastaların tanısı Uluslararası Behçet Hastalığı Çalışma Grubu kriterlerine göre konuldu. Tüm hastalara FFA uygulandı. Hastaların cinsiyeti, yaşı, hastalık süresi, oküler bulgular, FFA bulguları, oküler komplikasyonlar ve görme keskinliği bilgileri toplandı.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı 32.54 ± 9.45 (19-48) yıldı. Toplam olguların 57'si (%5.8) erkek, 47'si (%4.2) kadındı. Oküler tutulum olguların %73,1'inde bilateral, %26,9'unda ise unilateraldi. En sık görülen oküler bulgu %54,4 ile panüveitti. En sık görülen FFA bulgusu ise %81.1 ile optik disk kaçağıydı. Ön üveit oranı %12,7 iken, arka üveit oranı %32 idi. Görme keskinliği 0.5 veya daha yüksek olan gözlerin oranı %67.2, görme keskinliği 0.5 ile 0.1 arasında olanların oranı %21.1 ve görme keskinliği 0.1 veya daha düşük olanların oranı %11.6 idi.

Sonuç: OBH'nda en sık görülen oküler bulgu panüveit, en sık görülen FFA bulgusu ise optik disk kaçağıdır. FFA, OBH'ndaki retinal komplikasyonların tanı ve takibinde önemli rol oynar.

Anahtar kelimeler: Fundus fluorescein anjiyografisi, Oküler Behçet Hastalığı, Üveit.

Highlights

- Detection of ocular findings in ocular Behçet's disease is important in the follow-up and treatment of the disease.
- Fundus fluorescein angiography has an important role in the evaluation of retinal findings in ocular Behçet's disease.

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Introduction

Behçet's disease (BD) is a chronic, multisystemic inflammatory disorder characterized by oral and genital ulcers, intraocular inflammation, and specific skin lesions. Less commonly, it can also involve the joints, gastrointestinal system, and nervous system. The disease follows a geographical distribution along the ancient Silk Road, extending from Japan to the Mediterranean region, with the highest incidence observed in Türkiye (1). BD typically begins in the second and third decades of life and, with decreasing disease activity in later years, follows a pattern of remission and relapse (2). The course and severity of the disease vary from person to person (2). While the exact etiology of BD remains unclear, it is generally accepted that in genetically predisposed individuals, environmental factors trigger an irregular immune response that leads to vascular damage in most organ systems (3).

The common histopathological lesion in all organ systems affected by BD is occlusive vasculitis. The primary pathological findings of the disease include the accumulation of lymphomononuclear cells around blood vessels, swelling or proliferation of endothelial cells, partial occlusion of small vessels, and fibrinoid degeneration (4). Due to the wide clinical spectrum of the disease, the lack of a laboratory method that can definitively establish the diagnosis, and sometimes the absence of typical clinical features or the involvement of multiple organ systems, diagnosing BD can be challenging. Studies conducted in countries along the Silk Road have shown a marked association with HLA-B51 positivity in Behçet's patients, while no such association is observed in Western countries (5). Fluorescein angiography (FFA) in BD with posterior segment involvement can reveal dye leakage from retinal arteries, veins, and capillaries, providing valuable information about the retinal vascular system. FFA is essential for identifying primary retinal inflammation and for detecting abnormalities such as dye leakage from retinal vessels secondary to uveitis, retinal vein branch occlusion (RVO), retinal ischemia, neovascularization, macular edema, and macular ischemia (6).

Ocular Behçet's disease (OBD) is typically characterized by bilateral non-granulomatous panuveitis and retinal vasculitis, with isolated anterior uveitis and unilateral involvement being rare (7). Recurrent posterior uveitis attacks can lead to irreversible damage in the posterior segment and permanent vision loss (8). Retinal vasculitis is a major cause of vision loss in OBD (9). Recurrent retinal vasculitis attacks can lead to permanent sequelae. Secondary to occlusive vasculitis, RVO and, rarely, central retinal artery and vein occlusions can occur (9). In males and young adults, involvement is more frequent, and the disease course is more severe, whereas in females and older individuals, involvement is less frequent, and the disease course is milder (5). In the advanced stages of the disease, there may be increased tortuosity of retinal vessels, retinal ischemia, and consequently optic disc neovascularization (NVD), retinal neovascularization (NVE), macular edema, and diffuse retinal edema (4).

In our study, we aimed to identify ocular findings associated with OBD, their frequency, and the characteristics of FFA.

Material and Methods

Study design

The data of 104 patients diagnosed with OBD and followed up at our clinic between January 1996 and December 2006 were retrospectively reviewed. Patients with systemic diseases such as diabetes mellitus, hypertension, coronary heart disease, other rheumatologic diseases, and pregnancy, as well as those with ocular conditions such as corneal scarring, corneal dystrophy, glaucoma, diabetic retinopathy, and age-related macular degeneration, were excluded from the study. Patients with unknown follow-up durations and incomplete data were also excluded. A detailed medical history was taken from each patient. Best-corrected visual acuity was measured using the Snellen chart, and intraocular pressures were measured with a Goldman applanation tonometer. Anterior segment examinations were performed using slit-lamp biomicroscopy, and fundus examinations were conducted with a 90 diopter lens. The patients' ages and genders were recorded. Cases with iridocyclitis were classified as anterior uveitis, while cases with vitritis, retinal vasculitis, and retinitis without iridocyclitis were classified as posterior uveitis. Cases with involvement of both anterior and posterior segments were classified as panuveitis. The follow-up durations were recorded in months. The diagnostic criteria for ocular Behçet’s disease were evaluated according to the 2014 International Criteria for Behçet’s Disease (ICBD). The diagnostic criteria and scoring system included: ocular

involvement (2 points), anterior/posterior uveitis, retinal vasculitis, chorioretinitis, papilledema (presence of any of these findings), oral aphthous lesions (2 points), recurrent oral aphthous ulcers at least three times per year, genital ulcers (2 points), recurrent genital aphthous lesions, cutaneous findings (1 point), papulopustular lesions, erythema nodosum-like eruptions, neurological involvement (1 point), parenchymal central nervous system involvement, venous sinus thrombosis, vascular manifestations (1 point), venous thromboembolism, superficial thrombophlebitis, arterial thrombosis, aortic and pulmonary aneurysms, and a positive pathergy test (1 point). Diagnosis is confirmed for cases with a total score of 4 or more (ocular involvement was a prerequisite). This scoring system is based on the results of a multicenter study involving 27 countries, which demonstrates high sensitivity and specificity (10). During each follow-up visit, FFA (Zeiss FF 450 / Visupac) was performed on all patients. In FFA, increased hyperfluorescence in the late phase at the optic disc (OD) was defined as OD leakage. Retinal vasculitis was defined by leakage, staining, and occlusion in retinal vessels. Retinitis was defined as inflammation in the retina. OD edema was identified by hyperfluorescent appearance at the OD in FFA. Macular edema was defined by increased hyperfluorescence in the macula on FFA. New vessel formation at the optic disc was described as NVD, and new vessel formation in the retina was described as NVE. RVO was defined by localized hemorrhage in the retina. Central retinal artery occlusion (CRAO) was defined by the typical "Japanese flag" appearance in the macula and non-perfusion.

Statistical analysis

Statistical evaluations of the study were performed using SPSS 22.0 software. The normality of distribution was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages. Measurable data that met the parametric conditions were expressed as mean ± standard deviation.

Ethical Approval

This study approval was obtained from the Uludag University Faculty of Medicine, Ethics Committee (number: session: 17/2007 decision no: 12 date: 23.10.2007). This study was conducted retrospectively. Therefore, no consent form was obtained. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

A total of 104 patients (208 eyes) diagnosed with OBD were included in the study. Of these patients, 57 (54.8%) were male and 47 (45.2%) were female. The mean age was 32.54±9.45 years (ranging from 15 to 64 years). Ocular involvement was detected in 180 eyes (86.53%) of the 104 patients (208 eyes) diagnosed with OBD. Demographic characteristics and baseline characteristics are presented in Table 1.

Table 1. Demographic Characteristics and Key Features

Variables		Values
Age, years		32.54 ± 9.45
Gender, (%) **Male**		57 (54.82)
Female		47 (45.19)
OBD Number of case		104 (208)
Follow-up period, months		46.4 ± 26.3

Abbreviations: OBD: Ocular Behçet Disease, SD: standard Deviation

Of all cases, 28 (26.9%) had unilateral involvement, and 76 (73.1%) had bilateral involvement. The distribution of involvement types, including anterior, posterior, and panuveitis, is shown in Table 2.

Table 2. Distribution of Involvement Types in Ocular Behçet's Disease According to Uveitis

Types of Involvement	Anterior uveitis, n (%)	Posterior uveitis, n (%)	Panuveitis, n (%)

Unilateral (n:28; 26.9%)	5 (17.8)	9 (32.1)	14 (50)
Bilateral (n: 76; 73.1%)	9 (11.8)	25 (32.8)	42 (55.2)

The most common ocular finding was panuveitis, observed in 98 eyes (54.4%). The most common FFA finding was optic disc (OD) leakage, detected in 146 eyes (81.1%). Anterior uveitis was present in 23 eyes (12.7%), while posterior uveitis was observed in 59 eyes (32%). Panuveitis was present in 98 eyes (54.4%). The frequencies of retinal vasculitis, macular edema, retinitis, optic disc edema, RVO, optic disc hyperemia, increased tortuosity of retinal vessels, diffuse retinal edema, CRAO, dye leakage from retinal vessels, new vessel formation in the retina (NVE), and new vessel formation at the optic disc (NVD) were as follows: 28.8%, 17.7%, 13.3%, 6.62%, 1.12%, 10.5%, 7.75%, 4.45%, 0.55%, 26.2%, 6.72%, and 2.23%, respectively (Table 3).

Visual acuity results showed that 121 eyes (67.2%) had a visual acuity of 0.5 decimal or higher, 38 eyes (21.1%) had a visual acuity between 0.5 decimal and 0.1 decimal, and 21 eyes (11.6%) had a visual acuity of 0.1 decimal or lower **(Table 4)**.

Table 3. Ocular and Fundus Fluorescein Angiography Findings in Ocular Behçet's Disease

Ocular Findings	Number of affected eyes	%
Anterior uveitis	23	12.7
Posterior uveitis	59	32.7
Panuveitis	98	54.4
Retinal Vasculitis	52	28.8
Macular edema	32	17.7
Retinitis	24	13.3
Optic disc edema	12	6,62
Retinal vein branch occlusion	2	1,12
Optic disc hyperemia	19	10,5
Increased tortuosity of retinal vessels	14	7,75
Diffuse retinal edema	8	4,45
Central retinal artery occlusion	1	0,55
Leakage from the optic disc	146	81.1
Dye leakage from retinal vessels	47	26.2
Peripheral retinal neovascularization	12	6.72
Optic disc neovascularization	4	2.23

Table 4. Distribution of Ocular Behçet Disease Cases According to Visual Acuity

Visual Acuities (Decimal)	Number of Affected Eyes (n:180)	%	Visual Acuities (Decimal)
≥ 0.5	121	67.2	≥ 0.5
0.1-0.5	38	21.1	0.1-0.5

Discussion

BD is a chronic, systemic inflammatory disorder with multi-organ involvement. The disease typically presents in the second and third decades of life, and its severity tends to decrease with age (11). Ophthalmic findings of Behçet's disease can be listed as follows: 1- Anterior uveitis 2- Posterior uveitis 3- Panuveitis 4- Retinal vasculitis 5- Retinal vein occlusion 6- Optic disc edema 7- Retinitis 8- NVD, NVE

In our study, we found the rate of anterior uveitis to be 12.7%, posterior uveitis to be 32.7%, and panuveitis to be 54.4%. Similarly, in the study by Tutkun et al. involving 880 cases of ocular BD, the rates of anterior uveitis, posterior uveitis, and panuveitis were reported as 11%, 28.8%, and 60.2%, respectively (12). In the study by Khairallah et al. conducted in Tunisia, the rates of anterior uveitis, posterior uveitis, and panuveitis were reported as 4.5%, 34.2%, and 61.3%, respectively (13). In contrast to our study, Khairallah et al. reported a lower rate of anterior uveitis. This difference could be attributed to geographical variations and differences in sample size. Mohammad et al. reported anterior uveitis in 17% of cases and posterior uveitis in 25% (14). Similarly, Accorinti et

al. conducted a study with 2211 OBD cases in Italy and reported anterior uveitis in 11.4%, posterior uveitis in 20.8%, and panuveitis in 66.8% (15).

FFA is considered the gold standard imaging technique in the diagnosis and monitoring of uveitis in ocular BD. It is crucial for monitoring retinal inflammatory processes associated with posterior uveitis (16). In our study, the most common FFA finding was OD leakage (81.1%). Gedik et al. reported the rate of OD leakage in FFA in OBD cases as 89.8%, while Keorochana et al. reported it as 74% (17,18). Similarly, in our study, the OD leakage rate was 81.1%.

Khairallah et al. reported retinal vasculitis in 80.2% of OBD cases (13). Tutkun et al. reported the rate of retinal vasculitis as 89% (12). Keorochana et al. reported a rate of 42.5% (18). In our study, however, the rate of retinal vasculitis in OBD was 28.8%. This difference is likely due to the smaller sample size in our study. Gedik et al. reported the rate of leakage from retinal vessels as 73.5%, and Yu et al. reported it as 73.4% (17,19). In our study, the rate of leakage from retinal vessels was 26.2%. Leakage from retinal vessels is common, particularly during active attacks in patients with OBD. We believe that this difference may stem from the fact that our study did not focus on active phase of the disease.

In our study, the rate of macular edema in OBD cases was 17.7%. Similarly, Khairallah et al. reported a rate of 19.8%, and Keorochana et al. found 11% (13,18). However, Tutkun et al. reported a much higher rate of macular edema (44.5%) (12). We believe this difference could be due to the lack of optical coherence tomography (OCT) in our study, leading to some cases of macular edema being overlooked.

New vessel formation (NVD) is an indicator of poor visual prognosis in OBD. Visual outcomes associated with NVD remain poor, even with vitrectomy and immunosuppressive agents (20). Tutkun et al. reported the rates of NVD and NVE as 4.3%, while Khairallah et al. reported them as 5.4% (12,13). In line with these findings, we found the rate of NVD in our study to be 2.23%. We also found the rate of retinal vein branch occlusion (RVDT) in OBD cases to be 1.12%, which is consistent with the literature (12,13,18).

Central retinal artery occlusion (CRAO) is very rare in OBD. Özdal et al. reported only one case of CRAO (0.4%) in their study (21). CRAO in Behçet's disease has been reported in the literature as isolated case reports. In our study, one eye (0.55%) had CRAO. Khairallah et al. reported that 57.7% of Behçet's uveitis patients had visual acuity of 20/40 or better, 21.1% had visual acuity between 20/200 and 20/40, and 21.1% had visual acuity of less than 20/200 (13). In our study, the percentage of eyes with visual acuity of 0.5 or better was 67.2%, while 21.1% had visual acuity between 0.1 and 0.5, and 11.6% had visual acuity of 0.1 or worse.

Study limitations

Limitations of our study include its retrospective design, which may have led to missing or incomplete data; the small sample size; the lack of optical coherence tomography for diagnosing and classifying macular edema; the absence of records on systemic medication use; and the inclusion of only those patients with ocular manifestations of Behçet's disease who visited the ophthalmology department.

Conclusions

In conclusion, the most common ocular finding in OBD is panuveitis, and the most frequent FFA finding is OD leakage. FFA plays an important role in diagnosing and monitoring posterior uveitis and secondary complications in OBD. It is an essential imaging technique for monitoring inflammatory processes in the posterior segment and preventing irreversible visual function loss due to complications in ocular Behçet's disease.

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Data Availability: *The data used to support the findings of this study are available from the corresponding author upon request*

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Original Article

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Comparing Knowledge and Attitudes on Cancer Screening with and without Family Cancer History

Ailesinde Kanser Tanısı Olan ve Olmayan Bireylerin Kanser Tarama Programlarına Yönelik Bilgi ve Tutumlarının Karşılaştırılması

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Abstract

Background: This study aims to compare participation rates in cancer screening programs, as well as knowledge and attitudes toward these programs, among individuals with and without a family history of cancer. It also examines sociodemographic factors and explores potential reasons for any observed differences.

Material and Methods: A questionnaire consisting of 52 questions was administered to participants aged 30–70. The questionnaire included sociodemographic data, the Cancer Knowledge Scale, and the Cancer Attitude Scale. A total of 420 participants completed the survey, with 210 individuals having a family history of cancer and 210 without.

Results: The participation rate in cancer screening tests was significantly higher among individuals with a family history of cancer, 34.3% compared with those without 19.5% ($p = 0.001$). The mean score on the knowledge scale was 19.6 ± 4.5 for individuals who participated in screening tests, compared to 16.6 ± 5.7 for those who did not ($p < 0.001$). The mean score on the attitude scale was 69.0 ± 8.3 for individuals who participated in screening tests, compared to 66.8 ± 9.2 for those who did not ($p = 0.025$). A moderate positive correlation was found between knowledge and attitude scale scores for all participants ($r = 0.374$, $p < 0.001$).

Conclusions: Individuals with a personal or family history of cancer exhibit higher participation rates in cancer screening programs. Furthermore, increased knowledge about screenings is associated with more positive attitudes toward them, indicating that targeted public
education initiatives are warranted to bolster screening uptake.

Keywords: 'Health Knowledge, Attitudes, Practice', 'Early Detection of Cancer', 'Colonoscopy', 'Mammography', 'Papanicolaou Test'

ÖZ

Amaç: Ailesinde kanser tanısı olan ve olmayan bireylerin kanser tarama programlarına katılımlarının, kanser tarama programı hakkındaki bilgi ve tutumlarının sosyodemografik veriler ışığında karşılaştırılması ve olası nedenlerinin irdelenmesi amaçlanmaktadır.

Gereç ve Yöntem: Sosyodemografik veriler, Kanser Taramalarına Yönelik Bilgi Ölçeği ve Kanser Taramalarına Yönelik Tutum Ölçeğinden oluşan toplamda 52 soruluk anket 30–70 yaş katılımcılara yapılmıştır. Ailesinde kanser öyküsü olan 210 ve ailesinde kanser öyküsü olmayan 210 kişiye ulaşılarak toplamda 420 anket verisi ile çalışma sonlandırılmıştır.

Bulgular: Tarama testlerine katılım oranı ailede kanser öyküsü olanlarda %34,3 iken, ailede kanser öyküsü olmayanlarda %19,5'tir ($p = 0,001$). Tarama testi yaptıranlarda bilgi ölçeği puan ortalaması 19,6 ± 4,5 iken yaptırmayanlarda 16,6 ± 5,7'dir ($p < 0,001$). Tarama testi yaptıranlarda tutum ölçeği puan ortalaması 69,0 ± 8,3, yaptırmayanlarda ise 66,8 ± 9,2'dir ($p = 0,025$). Bilgi ve tutum ölçek puanları arasında tüm bireylerde anlamlı orta düzeyde pozitif korelasyon bulunmuştur ($r = 0,374$, $p < 0,001$).

Sonuç: Ailesinde ya da kendisinde kanser tanısı olan bireylerin kanser taramalarına katılım oranlarının da daha yüksek olduğu gözlemlenmiştir. Bireylerde taramalara yönelik bilgi düzeyi arttıkça tutumunda aynı şekilde iyileştiği istatiksel olarak ortaya konulmuştur. Bu durum taramaya yönelik tutumunun iyileşmesinin bilgi düzeyinin artırılmasıyla mümkün olduğunu bizlere göstermektedir. Bilgi düzeyinin artırılması içinse toplumun eğitilmesi esastır.

Anahtar kelimeler: 'Sağlık Bilgisi, Tutum, Uygulama', 'Kanserin Erken Teşhisi', 'Kolonoskopi', 'Mamografi', 'Papanicolaou Testi'

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Highlights

- Cancer incidence was higher among individuals with a family cancer history.
- Female participants demonstrated higher knowledge and screening engagement.
- A positive association was observed between knowledge and screening behavior.

Introduction

Cancer is the second leading cause of death worldwide and in Turkey, following cardiovascular diseases. In 2022, approximately 9.7 million people died from cancer globally, and cancer accounted for one in every six deaths (1,2). Increasing awareness of cancer screening programs is one of the most effective strategies in the fight against cancer (3). In Turkey, screening programs for breast, cervical, and colorectal cancer are provided free of charge (4). To ensure the success of these programs, it is essential to screen 70% of the targeted population. According to data from the Ministry of Health of the Republic of Turkey, while 3.5 million cancer screenings were performed in 2020, 4.5 million individuals were included in the screening program in 2021 (3).

Family medicine serves as the primary point of contact within preventive health services and plays a vital role in the implementation of cancer screening programs. Educating the public about screening programs based on age groups and guiding them to the appropriate screenings are essential responsibilities. Specifically, closely monitoring individuals with a family history of cancer and including them in screening programs is of great importance (5,6).

This study aims to compare the knowledge and attitudes toward cancer screening in individuals with first, second and third degree relatives diagnosed with cancer, with those without a family history. Additionally, the study seeks to investigate the reasons behind these differences. With the understanding that increasing cancer screening rates will reduce late-stage cancer cases and related deaths, the goal is to raise awareness among the public about the importance of screening programs (7).

Material and Methods

Study design

This cross-sectional study was conducted with volunteer participants aged 30–70 year who sought care at the units under the Department of Family Medicine, Samsun University Faculty of Medicine (including the Family Medicine Outpatient Clinic, Complementary and Integrative Medicine Outpatient Clinic, Training Family Health Center, Home Healthcare Unit, Obesity Outpatient Clinic, Smoking Cessation Outpatient Clinic, and Palliative Care Service) between May 15 and October 15, 2024. This age range was selected because the cancer screening programs of the General Directorate of Public Health of the Ministry of Health of Turkey begin at age 30 and end at age 70 (4).

To determine the required size, data from the previous year was considered. The total number of individuals who applied to the units between May 15 and October 15, 2023, was 7.963. Based on sample size calculations, it was determined that a minimum of 367 participants would be needed to achieve a 95% confidence level with a 5% acceptable margin of error. To account for a potential 10% missing data (n = 37), the minimum target was set at 404 participants, divided equally into a study group (n = 202) and a control group (n = 202). Ultimately, 210 participants with a family history of cancer and 210 without a family history were included, resulting in a total of 420 participants. All eligible participants were enrolled in the study and successfully completed the survey. Those with a family history of cancer were also considered according to their first-degree (mother, father, child), second-degree (sibling, grandfather, grandmother, grandchild), and third-degree (uncle, aunt, nephew, niece) relatives.

The questionnaire consisted of 12 sociodemographic questions and two standardized scales: the Cancer Screening Knowledge Scale (CKS) and the short form of the Cancer Screening Attitude Scale (CAS). The sociodemographic variables were determined in accordance with findings from previous studies and models used in national demographic surveys. The CKS, a 25-item scale with a 3-point Likert-type response format (1 = True, 2 = False, and 3 = I do not know), was validated by Yıldırım Öztürk et al. (Cronbach's α = 0.89). Correct answers were scored as 1, while incorrect and "I do not know" answers were scored as 0. Three items with a negative meaning (A2, A10, A22) were reverse-coded. The total score ranged from 0 to 25 (8). The CAS, a 15-item Likert-type scale validated by Yıldırım Öztürk et al. (Cronbach's α = 0.95), assesses attitudes toward cancer screening. Responses

were scored on a scale from 1 to 5, with negative items (B10, B11, B12, B13, B14, B15) reverse coded. The total score ranged from 15 to 75 (9).

Participants completed a 52-question questionnaire using the face-to-face interview method, which took an average of 20 minutes. Each participant was enrolled only once to prevent data duplication. Identity information was not requested to ensure anonymity. Participants were informed that the data would be used solely for scientific purposes and provided their consent. No benefits were provided to participating physicians.

Statistical analysis

Data analysis was performed using SPSS version 28, with R Studio used for verification and Z-diff correlation analysis. The Kolmogorov–Smirnov test and Skewness–Kurtosis values were used to assess normality. Descriptive statistics (mean and standard deviation) were calculated for continuous variables that followed a normal distribution. Age groups were classified as 30–39, 40–49, 50–59, and 60–69 year, due to differences in the types of cancer screening offered at each age. The Student's t test was used to compare parametric differences between two independent groups, while the one-way ANOVA test was used for comparisons involving more than two groups. The Tukey test was employed for post hoc analyses, as the variances were homogeneous. The Bonferroni correction was applied to p values. The illiterate group was excluded from the one-way ANOVA test for education level. The Pearson correlation test was used to assess the correlation between two parametric variables, and Fisher's Z transformation was used to evaluate differences in correlations between groups. Categorical data were presented as frequency distributions, and the chi-square test was applied. p values <0.05 were considered statistically significant.

Ethical Approval

For this study was granted by the Samsun University Non-Interventional Clinical Research Ethics Committee on May 8, 2024 (decision number 2024/9/2). The study title was revised and re-approved by the committee on October 9, 2024 (decision number 2024/18/12). Informed consent was obtained from all participants.

Results

A total of 420 participants, 210 with a family history of cancer and 210 without, were included in the study. The average age of individuals with a family history of cancer was 45.8 ± 10.0 year while the average age of individuals without a family history of cancer was 46.8 ± 10.4 year (p = 0.304). The most frequent age group among those with a family history of cancer was 40–49 year (31.9%), while 33.8% of individuals without a family history of cancer were also in the 40–49 age range (p = 0.697). Regarding participation in screening tests, 34.3% (n = 72) of individuals with a family history of cancer underwent screening, compared to 19.5% (n = 41) of individuals without a family history of cancer (p = 0.001). The distribution of sociodemographic characteristics and responses to the screening program based on family history of cancer is shown in **(Table 1).**

Table 1. Sociodemographic by Family History

Characteristic	**Those with a family history of cancer, *n*(%)**		**Those without a family history of cancer, *n*(%)**		***p*/*x*2 value**
Sex					
Male	77	(36.7)	103	(49.1)	0.010/6.572
Female	133	(63.3)	107	(50.9)	
Age (year)					
30–39	66	(31.4)	56	(26.7)	
40–49	67	(31.9)	71	(33.8)	0.697/1.435
50–59	54	(25.7)	55	(26.2)	
60–69	23	(11.0)	28	(13.3)	
Marital status					
Married	160	(76.2)	169	(80.5)	0.567/1.136
Single	28	(13.3)	23	(11.0)	
Widowed	22	(10.5)	18	(8.6)	

Educational status					
Primary education and below	41	(24.3)	56	(26.7)	0.008/9.636
High school	40	(19.0)	61	(29.0)	
Higher education	119	(56.7)	93	(44.3)	
Income status					
Less than minimum wage Minimum	53	(25.2)	73	(34.8)	0.009/9.488
wage-poverty line	61	(29.0)	71	(33.8)	
Above the poverty line	96	(45.7)	66	(31.4)	
Cancer history					
None	10	(4.8)	6	(2.9)	0.547/1.206
Past	196	(93.3)	201	(95.7)	
Current	4	(1.9)	3	(1.4)	
Screening participation					
Yes	72	(34.3)	41	(19.5)	0.001/11.63
No	138	(65.7)	169	(80.5)	5
Who suggested the screening test?					
Family physician	61	(29.0)	66	(31.4)	
Another doctor	33	(15.7)	25	(11.9)	0.878/1.785
Non-physician health professional	7	(3.3)	9	(4.3)	
Friend/Family	17	(8.1)	18	(8.6)	
Not recommended	55	(26.2)	58	(27.6)	
Other	37	(17.6)	34	(16.2)	

Participation in specific cancer screenings revealed that 13.7% (n = 22) of individuals over 50 year of age underwent fecal occult blood testing (FOBT) or colonoscopy, 35.1% (n = 59) of women over 40 year of age had mammography, and 22.9% (n = 55) of women over 30 year of age underwent Pap smear testing. Additionally, 3.3% of participants reported undergoing tests not included in the official screening program, such as computed tomography, hemograms, tumor markers, PSA, and ultrasound, mistakenly believing them to be part of the screening program. The distribution of screening tests performed, based on the target population, is provided in **(Figure 1).**

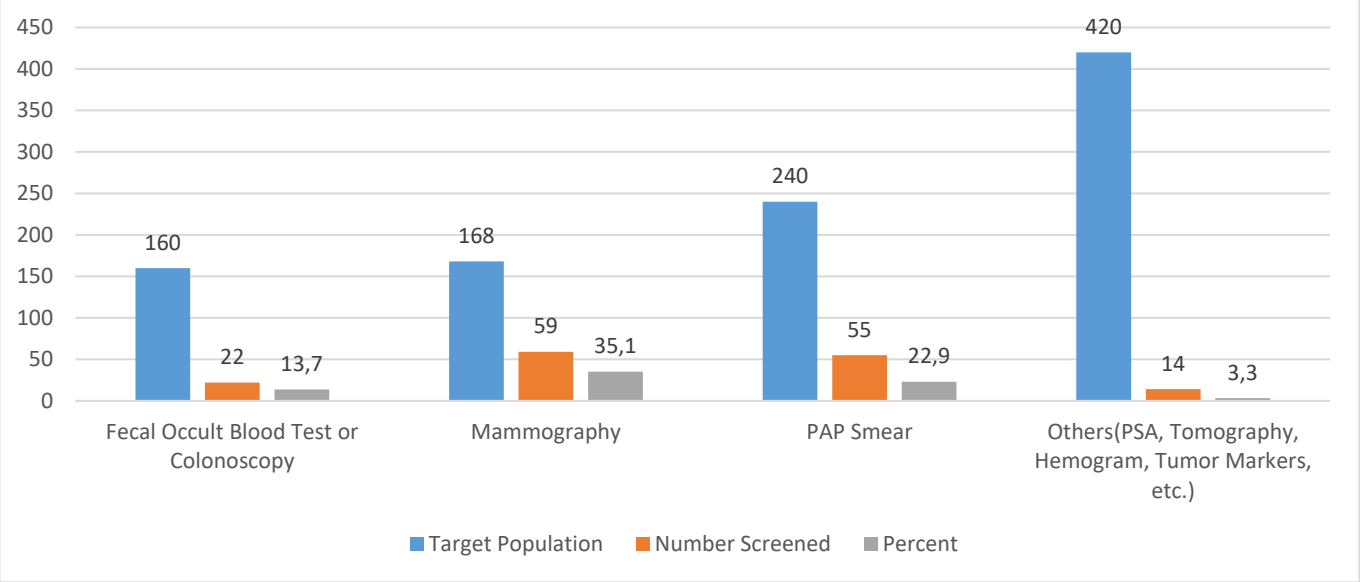

Figure 1. distribution of scans by target population

Among individuals with a current or past cancer diagnosis, the screening rate was 56.5% (n = 13), which was statistically significantly higher than the screening rate among individuals without a cancer diagnosis or history (p = 0.001). Cancer screening rates based on participants' family history are shown in **(Table 2).**

Table 2. Screening participation according to family history

Characteristic	Frequency of screening *n* (%)	*p*/*x*2 value
Individuals with no family history of cancer (*n* = 210)	41 (19.5)	0.001/11.635
Individuals with a personal diagnosis or history of cancer (*n* = 23)	13 (56.5)	0.001/10.853
Individuals with a first-degree relative diagnosed with cancer (*n* = 90)	34 (37.8)	0.009/6.886
Individuals with a second-degree relative diagnosed with cancer (*n* = 66)	22 (33.3)	0.200/1.646
Individuals with a third-degree relative diagnosed with cancer (*n* = 76)	27 (35.5)	0.061/3.507

Abbreviations: Because participants may have more than one relative diagnosed with cancer, the total exceeds 420.

The mean Cancer Screening Knowledge Scale (CKS) score for individuals without a family history of cancer was 17.0 ± 5.8. No statistically significant difference was found in the average CKS scores between those with and without a family history of cancer (p = 0.120). The Cancer Attitude Scale (CAS) score for individuals with a third-degree relative diagnosed with cancer was 69.0 ± 7.6, and a statistically significant difference was observed based on whether there was a cancer diagnosis in a third-degree relative (p = 0.047). The mean CKS and CAS scores based on family history are presented in **(Table 3).**

Table 3. Mean CKS and CAS scores according to family history

Characteristic	CKS score mean ± *SD*	*p*/*x*2 value	CAS score mean ± *SD*	*p*/*x*2 value
Individuals with no family history of cancer (***n*** = 210)	17.0 ± 5.8	0.120/1.558	66.8 ± 9.6	0.170/1.374
Individuals with a personal diagnosis or history of cancer (*n* = 23)	18.0 ± 4.2	0.563/0.579	69.3 ± 7.2	0.311/1.015
Individuals with a first-degree relative diagnosed with cancer (*n* = 90)	17.9 ± 5.2	0.332/0.972	67.9 ± 9.5	0.534/0.622
Individuals with a second-degree relative diagnosed with cancer (*n* = 66)	17.3 ± 5.0	0.926/−0.093	67.6 ± 6.7	0.878/0.153
Individuals with a third-degree relative diagnosed with cancer (*n* = 76)	18.2 ± 5.3	0.152/1.434	69.0 ± 7.6	0.047/2.002

Abbreviations: Because participants may have more than one relative diagnosed with cancer, the total exceeds 420.

A significant positive correlation was found between the CKS and CAS scores in all participants (n = 420; r = 0.374, p < 0.001). This positive correlation was also significant among individuals with a family history of cancer (n = 210; r = 0.429, p < 0.001) and among those without a family history of cancer (n = 210; r = 0.429, p < 0.001). The difference in correlation coefficients between individuals with and without a family history of cancer was not statistically significant (Z diff = 1.260, p = 0.208). The correlation between CKS and CAS scores, based on the presence or absence of a family history of cancer, is shown in **(Table 4).**

Table 4. Correlation of CKS and CAS Scores According to Family History

Characteristic	r	p	Z diff / p value
All individuals (*n* = 420)	0.374	<0.001	
Those with a family history of cancer (*n* = 210)	0.429	<0.001	1.260/0.208
Those without a family history of cancer (*n* = 210)	0.323	<0.001	

The mean CKS score for individuals who had undergone a screening test was 19.6 ± 4.5, compared with 16.6 ± 5.7 for those who did not undergo screening. This difference was statistically significant (p < 0.001). Similarly, the mean CAS score for individuals who had undergone screening was 69.0 ± 8.3, whereas those who did not undergo

screening had a mean score of 66.8 ± 9.2 (p = 0.025). The average CKS and CAS scores based on participant characteristics are shown in **(Table 5).**

Table 5. Mean CKS and CAS scores by sociodemographic

Characteristic	CKS score	p /t-F value	CAS score	p /t-F value
Sex				
Male	15.6 ± 6.2	<0.001/5.804	67.1 ± 9.8	0.503/0.670
Female	18.7 ± 4.5		67.7 ± 8.4	
Age (year)				
30–39	16.7 ± 6.2	0.145/1.806	67.8 ± 8.4	0.830/0.294
40–49	17.1 ± 5.4		67.4 ± 8.7	
50–59	18.3 ± 5.1		67.4 ± 9.5	
60–69	17.9 ± 4.9		66.4 ± 10.5	
Marital status				
Married	17.4 ± 5.4	0.205/1.588	67.8 ± 8.8	0.213/1.554
Single	16.3 ± 6.5		65.5 ± 10.0	
Widowed	18.3 ± 4.7		66.9 ± 9.9	
Educational status				
Primary education and below	16.5 ± 5.7	0.021/7.727	65.5 ± 11.3	0.476/1.486
High school	16.8 ± 5.3		67.7 ± 9.1	
Higher education	18.7 ± 4.9		69.2 ± 6.4	
Income status				
Less than minimum wage	16.8 ± 5.4	0.066/2.730	66.9 ± 9.7	0.082/2.511
Minimum wage-poverty line	16.9 ± 5.6		66.4 ± 9.9	
Above the poverty line	18.2 ± 5.4		68.6 ± 7.5	
Family history of cancer				
Yes	17.0 ± 5.8	0.120/1.558	68.0 ± 8.5	0.170/1.374
No	17.8 ± 5.3		66.8 ± 9.6	
Screening participation				
Yes	19.6 ± 4.5	<0.001/5.826	69.0 ± 8.3	0.025/2.248
No	16.6 ± 5.7		66.8 ± 9.2	

Discussion

Our study found that participants with a family history of cancer had a statistically significantly higher rate of having undergone at least one screening test compared with those without a family history of cancer. This finding is consistent with the results of Baycelebi et al. and Discigil et al., who also reported higher rates of screening test utilization among individuals with a family history of cancer (10,11). In contrast, two studies by Maras et al. and Achat et al. found no association between a family history of breast cancer and mammography use (12,13). This may be explained by the fact that the study conducted by Maras et al. in 2001 is relatively outdated, and approximately one-third of its participants were either illiterate or had only completed primary education (12). Similarly, the findings of the study by Achat et al., also conducted in 2001 in Australia, may have been influenced by its temporal context, cultural differences, and the age distribution of the participants, who were between 50 and 69 years of age (13). Although some studies show no association, our data support existing literature suggesting that a family history of cancer leads to increased utilization of preventive healthcare services.

In our study, the screening rate was found to be significantly higher, particularly among individuals with a personal cancer diagnosis or a first-degree relative diagnosed with cancer. This finding aligns with several studies indicating that individuals with a personal or family history of cancer are more likely to undergo screening tests (14,15,16). This is likely because individuals with prior cancer diagnoses or those with first-degree relatives diagnosed with cancer are more aware of the issue and more vigilant about their health check-ups due to concerns about cancer recurrence.

When asked about who recommended the screening test, the most common response was “family physician,” followed by “not recommended.” In contrast, the study by Ozsoyler et al. found that the most frequent source of information about cancer screenings was television, followed by family physicians and the Internet (17). Other studies have similarly identified television as the primary source of information, followed by healthcare professionals (11,18,19). While our study shows that the family physician is the most important source of advice, the fact that "not recommended" is the second most frequent answer may indicate a deficiency in informing the public and inviting them to screening programs.

In our study, a quarter of participants reported having undergone at least one cancer screening test. By comparison, Karakoyunlu Sen et al. and Uysal et al. found screening rates of 39.4% and 37.9%, respectively (20,21). Screening rates in our study were lower than those reported in these studies. Notably, our survey asked this question in an open-ended manner, and no responses indicating breast self-examination or clinical breast examination were provided. This suggests that when participants think of cancer screening, tests such as FOBT, colonoscopy, mammography, and Pap smear are the first to come to mind.

When examining screening rates by target population, it was found that 13.7% of individuals over 50 year of age had undergone FOBT or colonoscopy. In comparison, Bekdemir Ak et al. reported that 1.0% of participants had undergone FOBT and 2.1% had undergone colonoscopy; Ozsoyler found that 10.0% underwent FOBT and 4.3% underwent colonoscopy; Baycelebi et al. reported 10.8% for FOBT and 14.5% for colonoscopy; and Tas et al. found that 17% of participants had undergone one of the colorectal cancer screening tests (10,15,17,22). Colorectal cancer screening programs start at age 50, and the relatively low rates in the study by Bekdemir Ak et al. are attributed to the fact that only one-tenth of the participants were over 50 years old (4,15). In our study, 35.1% of women over 40 year of age had participated in mammography screening at least once. The literature shows a wide range of mammography participation rates, including 9.4%, 19.8%, 62.2%, and 23.9% (15,17,23,24). The high rate in Sahin et al.’s study is attributed to the fact that the study was conducted on healthcare professionals (23). In our study, the rate of Pap smear testing in women over 30 year of age was found to be 22.9%. In the literature, these rates vary, with reported values of 24.9%, 19.4%, and 51.3% (10,18,25). Akyuz et al.’s study, which focused on individuals aged 19–61, reported a higher Pap smear rate, likely because it was conducted in an obstetrics and gynecology outpatient clinic (25). According to 2022 data from the Turkish Statistical Institute, the mammography screening rate was 34.4%, while the Pap smear rate was 35.6% (26). It is noteworthy that the 2024 data did not show higher rates than those reported in 2022, indicating the need for increased focus on these areas.

No statistically significant differences were found in the total scores for CKS and CAS between individuals with a personal or family history of cancer and those without a family history. Ozsoyler et al. found a significantly higher rate of knowledge about cancer screening in individuals with a family history of cancer compared to those without (17). Supporting this view, another study found that individuals with a family history of breast cancer had better knowledge levels regarding breast cancer (16). Similarly, Yegenler’s research indicated that individuals with a personal history of cancer had more positive attitudes toward cancer screenings (27). In Acıkgoz et al.’s study,

individuals with cancer were found to have a higher level of cancer awareness (28). Our study also found a significant positive correlation between CKS and CAS scores, suggesting that as a person's level of knowledge about cancer screenings increases, their attitude toward cancer screenings also improves.

In our study, CKS scores were significantly higher with increasing education level, though no significant difference was found in CAS scores. Similarly, Bekdemir Ak et al. found that cancer screening knowledge scores increased with higher education levels (15). A study by Chali et al. showed that more positive attitudes toward cervical cancer screening was observed with higher education (29). A systematic review by Wools et al. revealed that lower education levels reduce participation in colorectal cancer screening (30). Individuals with higher levels of education tend to have better health awareness. This study also demonstrates that knowledge about cancer screenings is closely associated with educational level. Therefore, planning stepwise and needs-based educational programs targeting individuals with lower educational backgrounds is important for increasing awareness and participation rates in the general population.

Men utilize preventive healthcare services less than women (31,32). In our study, three-quarters of those who underwent screening tests were women and this difference was statistically significant. Our data support the notion that women benefit more from preventive healthcare services, and the lower utilization of healthcare services by men places them at a disadvantage. Globally, cancer mortality rates are higher in men than in women (33). In a study by Sahin, there were fewer male participants, and their total scores on the attitude scale toward cancer screenings were also lower (34). Our study indicates that women's level of knowledge regarding cancer screenings is statistically significantly higher than that of men. Another study found that men had higher awareness of breast cancer than women (35). The disparity in knowledge may be due to the greater number of screening programs available for women compared to men.

Individuals who undergo screening exhibit significantly higher levels of knowledge and more positive attitudes toward cancer screening compared to those who do not. Bekdemir Ak et al. found higher levels of knowledge among those who underwent screening in their study (15). Increasing public knowledge through education about screening programs can help improve attitudes and participation rates. Oruc et al. found that screening behaviors improved when individuals were informed by family medicine units (36). Primary care physicians play a crucial role in raising awareness and encouraging the public to participate in regular screening programs.

Study limitations

One limitation of our study is the lack of comparable data for the total CKS scores in literature, as this scale is relatively new. Other limitations are include being single-centered and cross-sectional design., and using Turkish language. Multicenter or longitudinal future studies are needed to close the gaps of our study. Additionally, due to the unavailability of individual-level raw data, we were unable to perform and present a scatterplot with a regression line for the correlation between CKS and CAS scores. This limits the visual and statistical exploration of the relationship between these two variables.

The novelty of using the CKS in this study also constitutes one of its strengths. Another strength is that this is one of the few studies to compare and examine knowledge and attitudes toward cancer screening based on whether participants have a family history of cancer.

Conclusion

In our study, we observed that individuals with a family or personal history of cancer had higher rates of participation in cancer screening programs. Similar to prior literature, participation rates in screening programs were found to be below the targeted level in our study. We statistically demonstrated that as individuals' knowledge about screenings increases, their attitudes toward them also improve, with a positive correlation. This suggests that enhancing attitudes toward screening can be achieved by increasing knowledge. To improve knowledge levels, public education is essential, and greater emphasis should be placed on educational initiatives related to preventive healthcare services.

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From past insights to future challenges: A global bibliometric analysis of hepatic steatosis (1980–2025)

Geçmişin çıkarımlarından geleceğin zorluklarına: Hepatik steatozun global bibliyometrik analizi (1980–2025)

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Abstract

Background: This study aimed to bibliometrically analyze publications on Hepatic Steatosis (HS) indexed in the Web of Science (WoS) database between 1980 and 2025, with the objective of identifying global research trends, leading authors, institutions, and countries, influential journals, collaboration networks, and emerging priority research areas.

Material and Methods: A total of 3,871 articles were evaluated. The scientific mapping of the HS literature was conducted using the Bibliometrix R package and its Biblioshiny interface.

Results: The number of publications on HS has increased rapidly over the past forty-five years, with research largely characterized by teamwork and international collaboration. Prof. Yu Li, Prof. Yuxiu Liu, and Asst. Prof. Hyunbae Kim emerged as the most prominent researchers, while Hepatology, Journal of Hepatology, and PLOS One were identified as the most influential journals. At the country level, China, the United States, and South Korea were the leading contributors. Keyword and thematic analyses highlighted a research focus on metabolic syndrome, inflammation, non-invasive diagnostic methods, and molecular mechanisms.

Conclusions: The findings reveal that HS research demonstrates multidisciplinary progress encompassing both fundamental pathophysiological processes and clinical applications. Research trends and collaboration structures indicate the field is becoming increasingly globalized with substantial scientific impact. In the future, metabolic disorders, the gut microbiota, and targeted molecular therapeutic strategies are expected to be prioritized research themes.

Keywords: Hepatic steatosis; bibliometric analysis; science mapping

ÖZ

Amaç: Bu çalışma, 1980–2025 yılları arasında Web of Science (WoS) veri tabanında yayımlanan Hepatic Steatosis (HS) konulu makaleleri bibliyometrik açıdan inceleyerek küresel araştırma eğilimlerini, önde gelen yazar, kurum ve ülkeleri, etkili dergileri, işbirliği ağlarını ve gelecekteki öncelikli araştırma alanlarını ortaya koymayı amaçlamıştır.

Gereç ve Yöntem: Analiz kapsamında 3871 makale değerlendirilmiştir. HS konusundaki literatürün bilimsel haritalaması, Bibliometrix R paketi ve Biblioshiny arayüzü kullanılarak gerçekleştirilmiştir.

Bulgular: HS alanında yayın sayısının son kırk beş yılda hızlı bir şekilde arttığı, araştırmaların büyük ölçüde ekip çalışması ve uluslararası işbirliği ile yürütüldüğü saptanmıştır. Prof. Yu Li, Prof. Yuxiu Liu ve Asst. Prof. Hyunbae Kim önde gelen araştırmacılar olarak öne çıkarken, Hepatology, Journal of Hepatology ve Plos One en etkili dergiler olarak belirlenmiştir. Ülkeler düzeyinde Çin, ABD ve Güney Kore lider konumdadır. Anahtar kelime ve tematik analizler, metabolik sendrom, inflamasyon, non-invaziv tanı yöntemleri ve moleküler mekanizmalar üzerine odaklanmayı göstermektedir.

Sonuç: Araştırma sonuçları, HS araştırmalarının hem temel patofizyolojik süreçleri hem de klinik uygulamaları kapsayan multidisipliner bir ilerleme sergilediğini ortaya koymaktadır. Araştırma eğilimleri ve işbirliği yapıları, alanın giderek globalleştiğini ve yüksek bilimsel etkiye sahip olduğunu göstermektedir. Gelecekte, metabolik bozukluklar, mikrobiyota ve hedefe yönelik moleküler tedavi stratejileri öncelikli araştırma konuları olarak öne çıkacaktır.

Anahtar kelimeler: Hepatik steatoz; bibliyometrik analiz; bilim haritalama.

Highlights

- HS research has risen markedly since 1980, supported by strong international collaboration.
- China, the USA, and South Korea lead the field.
- Future priorities include metabolic syndrome, inflammation, and non-invasive diagnostics.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most prevalent chronic liver disease and is strongly associated with metabolic risk factors such as obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia (1,2). Previously referred to as non-alcoholic fatty liver disease (NAFLD), this condition was redefined as MASLD following a 2023 terminology update, while its progressive form characterized by inflammation and fibrosis was designated as metabolic dysfunction-associated steatohepatitis (MASH) (3,4). The shift from NAFLD to MASLD was primarily motivated by the need to adopt a more inclusive and pathophysiologically accurate definition that emphasizes metabolic dysfunction rather than the mere exclusion of alcohol consumption (5). Furthermore, earlier proposals such as metabolic dysfunction-associated fatty liver disease (MAFLD) were also introduced in 2020, aiming to highlight metabolic risk factors (2). However, international consensus now favors MASLD, while some studies still use NAFLD or MAFLD, leading to heterogeneity in the literature (3).

MASLD encompasses a wide clinical spectrum ranging from simple steatosis to cirrhosis and represents a major public health concern due to both liver-related morbidity and cardiometabolic complications (6,7). Given this evolving terminology, the present study adopts the overarching concept of "hepatic steatosis (HS)" as a unifying term to systematically capture all relevant research regardless of the terminology used in different periods. This approach ensures consistency and allows for a comprehensive assessment of the global research landscape.

In recent years, the number of studies focusing on HS has increased substantially worldwide (8). However, the rapid expansion of the literature makes it challenging to systematically identify the most recent trends, research gaps, and leading contributors (9,10). In this context, bibliometric analyses provide a valuable approach to quantitatively assess the volume, impact, and collaborative networks of scientific studies published on a given topic (11,12). While several bibliometric studies have previously addressed NAFLD or MAFLD in isolation (13,14), to the best of our knowledge, no large-scale bibliometric analysis has yet been conducted that integrates the evolving terminology under the unified concept of HS. Therefore, this study not only fills this gap but also provides novel insights into how terminological transitions have influenced research output, citation impact, and scientific collaboration in the field.

The aim of this study is to bibliometrically analyze publications on HS indexed in the Web of Science Core Collection (WoS) database between 1980 and 2025, with the objective of identifying global research trends, leading authors, institutions, and countries, influential journals, and emerging future research directions.

Material and Methods

Study design

The literature search process on HS was structured based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Search Strategy (PRISMA-S) guidelines, which ensure the transparent and reproducible reporting of search strategies in systematic reviews (15). The filtering steps and selection process applied during the literature search are presented in detail in a flow diagram to ensure the methodological rigor and reproducibility of the study **(Table 1)**.

Table 1. Search strategy suitable for PRISMA-S and workflow of analysis

Stage	Description	Criteria / Filters	Number of Articles	Analysis
1. Database selection	Selection of database for bibliometric analysis and literature review	Web of Science	—	**Performance Analysis** Main Information Publications Annual Scientific Production and Citation Per Year Sources' Local Impact Most Local Cited Document Authors' Local Impact Countries' Scientific Production **Collaboration Network Analysis** Authors Network Analysis
2. Search date	Date of literature search	6.08.2025	—	
3. Search terms	Title Search	Hepatic Steatosis	6364	
4. Publication type filter	Selection of specific publication types	Article or Review Article	4175	
5. Index filter	Selection of specific indexes	SCI_EXPANDED OR ESCI	4168	
6. Language	Restriction of publication	English	4118	

filter	language			Institutions Network Analysis Countries Network Analysis **Word and Thematic Analysis** Word Cloud From Author's Keywords Trend Topics Thematic Map
7. Year filter	Exclusion of publications from the year 2025	1980 - 2024	3871	
8. Final dataset	Articles included in the analysis	Remaining after applying all filters above	3871	

The synonymous or closely related keywords were merged, with the terms following the comma consolidated under the term preceding the comma. For example: non-alcoholic fatty liver disease, nonalcoholic fatty liver disease; non-alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD); non-alcoholic fatty liver disease, NAFLD; endoplasmic reticulum stress, ER stress; high-fat diet, high fat diet; non-alcoholic steatohepatitis, nonalcoholic steatohepatitis; triglycerides, triglyceride; AMP-activated protein kinase, AMPK.

In this study, the WoS database, one of the most commonly used sources for bibliometric analyses and literature searches, was employed. Different databases vary considerably in their journal coverage, whereas WoS is among the most widely preferred academic resources for bibliometric research (16).

The data search was performed in the WoS database on August 6, 2025. In the subsequent stage, the retrieved records were refined and filtered. A total of 6,364 documents were initially identified under the title "Hepatic Steatosis." When restricted to the document types "Article OR Review Article," the number decreased to 4,175. Limiting the WoS index to "SCI-EXPANDED OR ESCI" yielded 4,168 documents, while restricting the language to "English" resulted in 4,118 documents. Since new publications continue to be indexed, articles published in 2025 were excluded, yielding a final dataset of 3,871 publications, which were included in the analysis.

For the analysis of the retrieved dataset, the Bibliometrix package was utilized. Bibliometrix is a recent open-source software developed in R, designed to perform science mapping and bibliometric analyses (12).

In this study, a total of 3,871 articles were analyzed in three sections. The first section presents a performance analysis of publications in the field of HS, the second section focuses on collaboration analysis, and the third section covers keyword and thematic analysis.

Ethical Approval

Ethics committee approval is not required for bibliometric studies.

Results

Performance Analysis

Figure 1 illustrates the overall profile of scientific output on HS. The dataset covers studies published between 1980 and 2024, comprising a total of 3,871 documents authored by 20,911 different researchers. Notably, only 25 publications were single-authored, indicating that research in this field is predominantly conducted through collaboration.

The publications included 983 references and received a total of 93,737 citations. This high citation count highlights the strong foundation upon which HS research is built and underscores the critical role of previous studies in shaping the field. The mean publication age was 8.3 years, reflecting that most of the research remains up-to-date and aligned with ongoing scientific developments.

The rate of international collaboration was 20.05%, demonstrating substantial contributions from multiple countries and confirming the global relevance of HS research. Each document was co-authored by an average of 8.21 researchers, further supporting the finding that the field is largely driven by teamwork.

The annual growth rate was calculated as 14.21%, underscoring the rapid increase in research activity and the growing scientific interest in HS. Moreover, each publication received an average of 43.37 citations, suggesting that studies in this domain hold significant influence within the scientific community.

Finally, a total of 5,475 author keywords were identified, indicating that HS research encompasses a broad spectrum of topics and involves in-depth exploration across various subfields. Collectively, these findings highlight the dynamic growth of the field, its extensive collaborative networks, and its considerable global scientific impact.

Figure 1. Main information publications

Figure 2 illustrates the annual scientific production on HS and the average number of citations per year between 1980 and 2024. The early period (1980–1990) was characterized by very limited output (1–5 publications annually) and low citation rates (<1), reflecting minimal scientific attention to HS during that decade.

From the mid-1990s onward, a gradual rise in both publications and citations was observed, with notable peaks in the late 1990s and early 2000s. By 2004, the number of publications reached 30 with an unusually high citation average (11.8), indicating increased visibility of HS in both clinical and basic science research. The subsequent years (2005–2010) showed a steady growth in publication numbers (50–80 annually), while citation averages stabilized around 6.

A sharp increase occurred after 2010, when annual outputs exceeded 100 papers. Although productivity expanded rapidly, citation averages gradually declined, suggesting that growth in quantity was not matched by proportional gains in research impact.

Since 2014, HS research has entered a "publication boom," peaking at 347 articles in 2022. However, citation averages have continued to decline, reaching 1.7 in 2024, partly due to the limited time for recent papers to accumulate citations. Overall, the data highlight an exponential increase in HS-related research over the past two decades, but also a decline in average influence. These trends indicate that future impactful studies will likely require innovative topics, multidisciplinary designs, and stronger methodological frameworks. The trend line analysis confirmed a strong fit ($R^2 = 0.9774$), validating the observed growth trajectory.

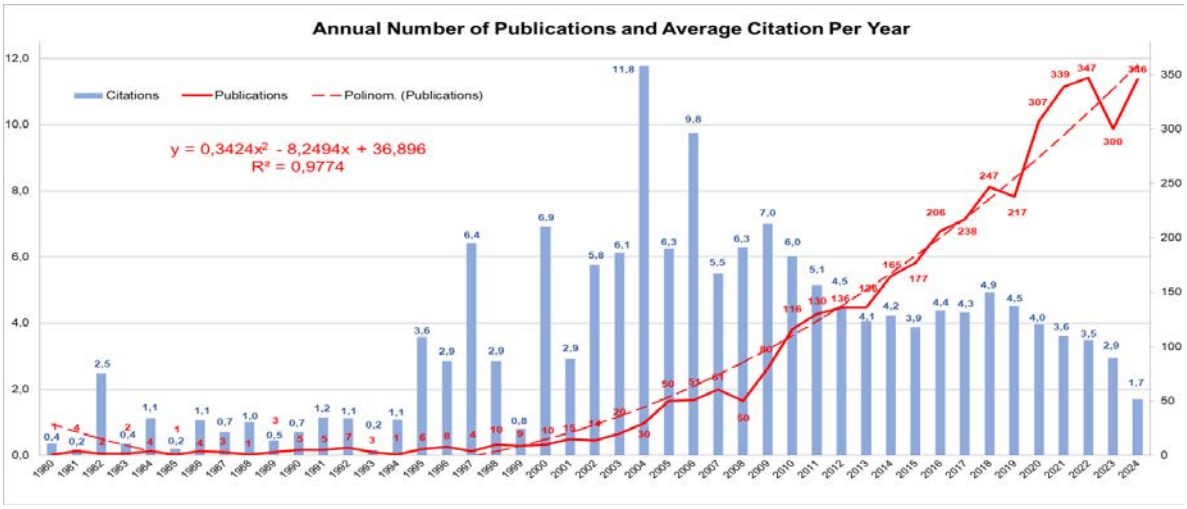


Figure 2. Annual scientific production and average citation per year

Table 2 presents the impact of leading researchers in the academic literature on HS, including various bibliometric indicators such as h-index, g-index, m-index, total citations (TC), number of publications (NP), and the year of first publication (PY_start). These metrics assess the influence of authors not only through their productivity but also through the citation impact of their contributions.

The h-index is a widely used measure of scientific productivity and academic influence, indicating that an author with an h-index of h has at least h publications, each cited at least h times (17). The g-index emphasizes the impact of highly cited works; an author has a g-index of g if their top g papers together received at least g^2 citations, thereby giving more weight to the most influential publications (18). The m-index is obtained by dividing the h-index by the number of years since the author's first publication, providing a fairer assessment for early-career researchers (17).

Among the most prominent contributors, Li Y (h-index= 27, TC= 3955, NP= 47) and Liu Y (h-index= 25, TC= 2087, NP= 33) stand out with both high productivity and strong citation performance. Having entered the field in the early 2010s (Li Y in 2010; Liu Y in 2011), they have maintained consistent impact, as reflected by their relatively high m-index values (1.688 and 1.667, respectively).

Kim H (h-index= 21, NP= 38) and Wang H (h-index= 20, NP= 30), who began publishing in 2008, also occupy a mid-to-high level in terms of both output and citation impact. Notably, Shulman GI, with only 21 publications, has achieved an exceptionally high citation count (TC= 3600, h-index= 18). His comparatively low m-index (0.75) is attributable to his earlier entry into the field (2002), highlighting his role as one of the pioneering contributors whose foundational studies shaped subsequent research.

Researchers from China and South Korea occupy a substantial proportion of the list. Names such as Zhang J, Zhang Y, Chen Y, Kim HJ, Lee JH, Li J, Liu J, Fan JG, Wang J, Chen X, Choi MS, and Choi Y have emerged as key actors since 2008, producing between 20–40 publications each with moderate-to-high citation impact. Particularly noteworthy are Zhang Y (m-index= 1.143) and Li L (m-index= 1.667), who, despite beginning their academic contributions more recently (2012 and 2017, respectively), have rapidly established significant influence in the field.

Table 2. Authors' local impact

Source	H-Index	G-Index	M-Index	TC	NP	TC/NP	PY_start
Hepatology	62	90	1.771	14737	90	163.74	1991
Journal Of Hepatology	44	55	1.467	6546	55	119.02	1996
Plos One	35	59	2.059	3992	98	40.73	2009
Scientific Reports	29	45	2.231	2453	87	28.20	2013
Diabetes	28	34	1.12	4696	34	138.12	2001
Nutrients	27	41	2.25	1926	77	25.01	2014
Journal Of Biological Chemistry	25	33	0.962	3937	33	119.30	2000
Am. J. Physiol. Endocrinol. Metab.	24	34	1.091	3018	34	88.76	2004
Journal of Lipid Research	24	40	1.043	2383	40	59.58	2003
Journal of Nutritional Biochemistry	23	39	1.211	1639	39	42.03	2007
Am. J. Physiol. Gastrointest. Liver Physiol.	22	32	1.048	1897	32	59.28	2005
Liver International	22	39	1.1	1550	43	36.05	2006
Food & Function	21	29	1.615	954	42	22.71	2013
J. Gastroenterol. Hepatol.	20	31	0.8	1804	31	58.19	2001
Molecular Nutrition & Food Research	20	28	1.111	1136	28	40.57	2008
J. Agric. Food Chem.	19	28	1.118	995	28	35.54	2009
Radiology	19	24	0.864	2853	24	118.88	2004
World Journal of Gastroenterology	19	27	0.704	1394	27	51.63	1999
Biomedicine & Pharmacotherapy	18	27	1.8	783	32	24.47	2016
Frontiers In Pharmacology	18	27	1.636	735	28	26.25	2015

Abbreviations: NP = Number of publications, TC = Total citations, TC/NP = Citations per paper, PY_start = Publication year starting Am. J. Physiol. Endocrinol. Metab.: American Journal Of Physiology-Endocrinology And Metabolism, Am. J. Physiol. – Gastrointest. Liver Physiol.: American Journal of Physiology-Gastrointestinal and Liver Physiology, J. Gastroenterol. Hepatol.: Journal of Gastroenterology and Hepatology, J. Agric. Food Chem.: Journal of Agricultural And Food Chemistry.

Table 3 presents the most locally cited (LC) publications in the field of HS and compares their global citation (GC) performance. The table also includes the publication age (YYP), annual average local and global citations (LC/YYP and GC/YYP), and the local-to-global citation ratio (LC/GC), enabling an assessment of both field-specific impact and broader academic visibility.

The most influential publication in HS is Browning JD (2004, Hepatology), which ranks highest in both local citations (LC= 179) and annual global citation rate (GC/YYP= 136.86). This demonstrates exceptional influence both within and beyond the field (LC/YYP= 8.524; LC/GC= 6.23%), indicating that while the paper is widely cited, the majority of citations originate from outside the HS research community. Similarly, Browning's early works, including J Clin Invest (2004) and Szczepaniak (2005), show strong impact at both local and global levels (e.g., Szczepaniak GC/YYP= 62.75; LC/YYP= 6.20).

Notably, Bedogni (2006, BMC Gastroenterol) exhibits a very high annual global citation rate (GC/YYP= 114.53) with an LC/GC ratio of 5.01, suggesting that most citations come from outside the HS field, reflecting broader interdisciplinary influence.

The LC/YYP metric balances differences in publication age, highlighting that papers such as Browning (2004), Lee JH (2010), and Sasso (2010) maintain high annual citation rates within the field. Meanwhile, GC/YYP emphasizes which publications generate wide interdisciplinary recognition, with Browning, Bedogni, and Li Y standing out as highly influential beyond HS research.

Table 3. Most local cited documents

Document	YP	LC	LC/YYP	GC	GC/YYP	LC/GC Ratio%
Browning Jd. 2004. Hepatology	2004	179	8.524	2874	136.86	6.23
Browning Jd. 2004. J Clin Invest	2004	159	7.571	1730	82.38	9.19
Szczepaniak Ls. 2005. Am J Physiol-Endoc M	2005	124	6.200	1255	62.75	9.88
Lee Jh. 2010. Digest Liver Dis	2010	116	7.733	1112	74.13	10.43
Postic C. 2008. J Clin Invest	2008	114	6.706	978	57.53	11.66
Bedogni G. 2006. Bmc Gastroenterol	2006	109	5.737	2176	114.53	5.01
Sasso M. 2010. Ultrasound Med Biol	2010	107	7.133	666	44.40	16.07
Li Y. 2011. Cell Metab	2011	94	6.714	1433	102.36	6.56
Park Sh. 2006. Radiology	2006	82	4.316	419	22.05	19.57
Bellentani S. 2000. Ann Intern Med	2000	76	3.040	991	39.64	7.67
Bohte Ae. 2011. Eur Radiol	2011	72	5.143	417	29.79	17.27
Tang A. 2013. Radiology	2013	57	4.750	432	36.00	13.19
Lee Ss. 2010. J Hepatol	2010	56	3.733	297	19.80	18.86
Dasarathy S. 2009. J Hepatol	2009	52	3.250	487	30.44	10.68
Ferré P. 2010. Diabetes Obes Metab	2010	51	3.400	562	37.47	9.07
Idilman Is. 2013. Radiology	2013	51	4.250	318	26.50	16.04
Kammoun Hl. 2009. J Clin Invest	2009	48	3.000	601	37.56	7.99
Boyce Cj. 2010. Am J Roentgenol	2010	48	3.200	194	12.93	24.74
Purushotham A. 2009. Cell Metab	2009	46	2.875	931	58.19	4.94
Myers Rp. 2012. Liver Int	2012	46	3.538	281	21.62	16.37

Abbreviations: Year of Publication (YP). YYP= Year 2025-Year of Publication. Global Citations (GC). Local Citations (LC)

Table 4 assesses the bibliometric performance of the most influential journals in HS research. Key indicators include h-index, g-index, m-index, TC, NP, TC/NP, and PY_start, allowing a quantitative comparison of each journal's contribution to the field.The journals with the highest overall impact are Hepatology (h-index= 62, g-index= 50, TC= 14,737, TC/NP= 163.74) and Journal of Hepatology (h-index= 44, TC/NP= 119.02), which have published high-quality, widely cited HS research since the early 1990s (1991 and 1996, respectively).

In the mid-to-high impact group, Diabetes (TC/NP= 138.12) and Radiology (TC/NP= 118.88) are notable. Although total publication counts are relatively low (34 and 24), the per-article citation impact is substantial, reflecting strong interdisciplinary interest in HS within metabolic diseases and imaging research.

High productivity with moderate impact is observed in Plos One (NP= 98, TC/NP= 40.73) and Scientific Reports (NP= 87, TC/NP= 28.20). These open-access, multidisciplinary journals achieve large publication volumes, though

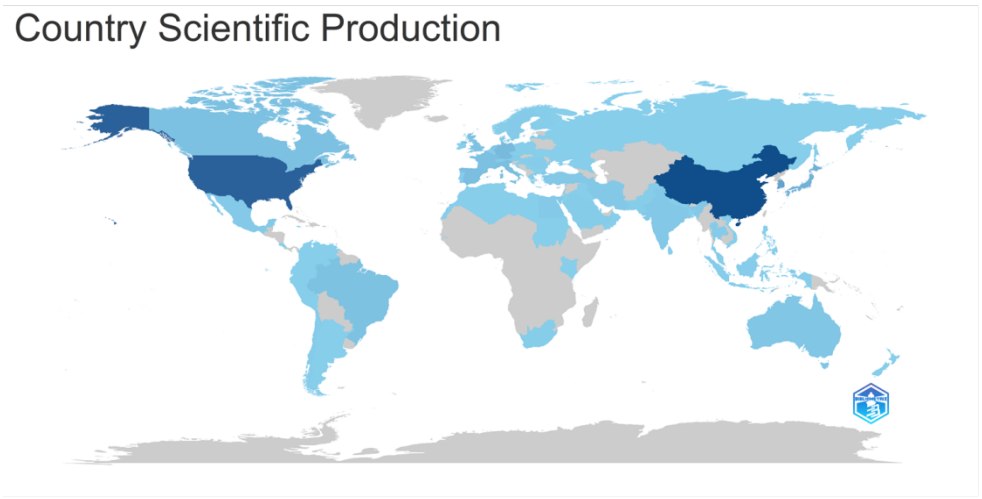
per-article citation impact remains lower than the field's leading journals. Similarly, Nutrients (NP= 77, TC/NP= 25.01) is frequently selected for nutrition-focused HS studies.
Specialized journals such as Journal of Nutritional Biochemistry (h-index= 23, TC/NP= 42.03), Liver International (h-index= 22, TC/NP= 36.05), and Journal of Gastroenterology and Hepatology (h-index= 20, TC/NP= 58.19) show a balanced profile in both productivity and citation impact.
Emerging platforms such as Biomedicine & Pharmacotherapy (PY\start= 2016, m-index=1.8) and Frontiers in Pharmacology (PY\start=2015, m-index=1.636) have demonstrated rapid early productivity, although per-article citation impact remains limited.
Overall, HS research achieves high visibility not only in hepatology-focused journals but also across metabolism, nutrition, biochemistry, imaging, and pharmacology journals. Core journals such as Hepatology and Journal of Hepatology provide high citation impact, whereas interdisciplinary journals like Diabetes and Radiology serve as strategically important venues for broader research dissemination.

Table 4. Sources' local impact

Element	H-Index	G-Index	M-Index	TC	NP	PY_start
LI Y	27	47	1,688	3955	47	2010
LIU Y	25	33	1,667	2087	33	2011
KIM H	21	38	1,167	1547	38	2008
WANG H	20	30	1,111	1235	30	2008
SHULMAN GI	18	21	0,75	3600	21	2002
WANG Y	17	32	0,81	1370	32	2005
ZHANG J	16	29	0,8	859	29	2006
ZHANG Y	16	32	1,143	1073	41	2012
CHEN Y	15	21	0,938	908	21	2010
KIM HJ	15	23	0,833	2017	23	2008
LEE JH	15	21	0,833	2192	21	2008
LI J	15	29	0,882	895	36	2009
LI L	15	23	1,667	545	27	2017
LIU J	15	26	0,938	879	26	2010
ZHANG L	15	29	0,833	883	30	2008
FAN JG	14	19	0,778	829	19	2008
WANG J	14	23	0,824	557	32	2009
CHEN X	13	20	0,867	630	20	2011
CHOI MS	13	14	0,722	732	14	2008
CHOI Y	13	17	0,867	584	17	2011

Abbreviations: NP: Number of publications, TC: Total citations, PY_start: Publication year starting

Figure 3 illustrates the scientific contributions of different countries in HS research. based on institutional affiliations reported by authors in their publications. It should be noted that these figures reflect the total institutional contributions rather than the number of individual authors or publications.
China leads with the highest institutional contribution (4,133), establishing itself as the global leader in HS research. The United States follows with 3,474 contributions, highlighting its strong research capacity in this field. In Asia, South Korea (1,320) and Japan (839) have made significant contributions. Among European countries, Germany (609), Italy (490), and Spain (479) are the most prominent. France, Canada, the United Kingdom, and Brazil fall within the mid-to-upper range of contributions (360–390), demonstrating considerable global involvement. The Netherlands (266) and Australia (233) also show high international visibility. Türkiye ranks at a moderate level with 173 institutional contributions, comparable to India (169) and Iran (167). Countries with lower levels of institutional contributions include Denmark, Mexico, Egypt, Austria, Switzerland, Thailand, Sweden, Saudi Arabia, and Israel.



Country	Frequency
CHINA	4133
USA	3474
SOUTH KOREA	1320
JAPAN	839
GERMANY	609
ITALY	490
SPAIN	479
FRANCE	390
CANADA	383
UK	361
BRAZIL	360
NETHERLANDS	266
AUSTRALIA	233
TURKEY	173
INDIA	169
IRAN	167
DENMARK	137
MEXICO	126
EGYPT	111
AUSTRIA	104
SWITZERLAND	99
THAILAND	90
SWEDEN	87
SAUDI ARABIA	69
ISRAEL	62

Figure 3. Countries' scientific production

Collaboration Network Analysis

Collaboration network analysis is a bibliometric approach used to map and quantify relationships among researchers, institutions, or countries, providing insights into the social structure of a research field. Nodes represent actors, while links denote co-authorship relationships. Network metrics such as centrality, density, and clustering help identify influential researchers and key collaboration hubs (19,20).

This method not only depicts current collaboration patterns but also highlights leading authors, pioneering institutions, and potential future partnerships, while indicating the level of scientific integration at regional and global scales (21). Publications on Hepatic Steatosis were retrieved from Web of Science, with author, institution, and country information extracted and analyzed using Biblioshiny, VOSviewer, CiteSpace, and Gephi.

The authors' collaboration network is shown in **Figure 4a.** Nodes represent researchers, and edges indicate collaborative links, with node size reflecting influence based on publication output and co-authorship intensity. The analysis included 33 nodes, and the Louvain algorithm was used for cluster detection. The red cluster is centered on Li Y and Zhang Y, showing dense collaborations with Liu Y, Zhang J, and Wang H, indicated by large node sizes representing high productivity and citation impact. The blue cluster is centered around Kim H, with strong links to Lee JH, Lee JY, Lee JM, Lee SG, Park JY, and Park J, reflecting intensive intra-group co-publication activity. The green cluster represents a collaboration network centered on Li J and Wang J, with strong links to Liu J and other green nodes. This cluster demonstrates both internal cohesion and significant connections with the purple cluster, reflecting active international and interdisciplinary collaborations. The purple cluster is centered on Wang Y, including authors such as Wang Q, Tsui PH, Chen X, and Zhang I. Strong links with the green cluster indicate that this group is both independently productive and engaged in inter-cluster collaborations. In the overall network, thick edges represent frequent and strong collaborations, while thin edges indicate less frequent co-authorship. Notably, bridges between the green–purple and green–red clusters highlight key collaborative pathways, illustrating the presence of robust regional and global research networks in Hepatic Steatosis.

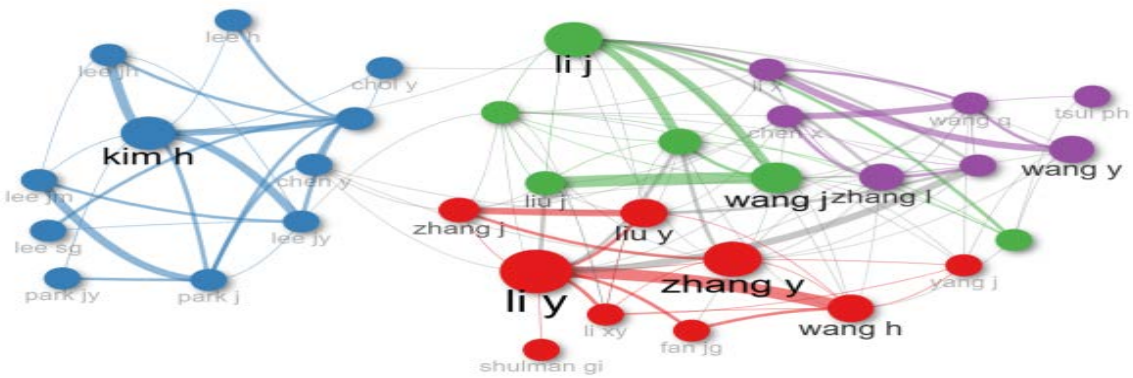


Figure 4a. Collaboration network analysis (Authors)

The Institutional Collaboration Network was analyzed using 20 nodes with the Louvain algorithm. Each node represents an institution, and multiple clusters are distinguished by color **(Figure 4b).** The University of California System occupies a central position with the highest centrality, indicating extensive collaborative activity and a major contribution to publication output. The US Department of Veterans Affairs and Veterans Health Administration (VHA) dominate the brown cluster, with thick connections reflecting high co-publication levels. Harvard University and Harvard University Medical Affiliates form the blue cluster, demonstrating a broad national and international collaboration network. The green cluster, centered on Yonsei University, Yonsei University Health System, and Seoul National University (SNU), represents an East Asia–focused research group with dense internal collaboration but limited links to other major centers. The orange cluster includes China-based institutions such as the Chinese Academy of Sciences and Shanghai Jiao Tong University, while the purple cluster highlights the University of Texas System and University of Texas Southwestern Medical Center. These clusters are active regionally but have fewer links compared to central global actors.

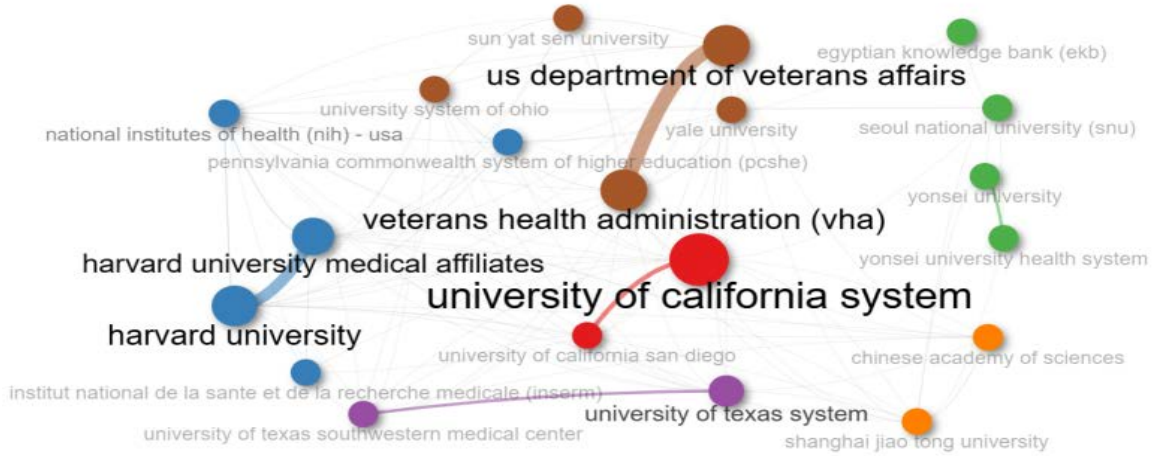


Figure 4b. Collaboration network analysis (Institutions)

The Countries Collaboration Network was analyzed using 30 nodes and the Louvain algorithm, with each node representing a country **(Figure 4c).** The network is divided into two main clusters. The red cluster includes Asia-Pacific and North American countries, with the USA and China as central actors. Thick edges between these two countries reflect high co-publication activity. The USA maintains strong connections with Canada, Japan, Korea, and Australia, while China collaborates with Türkiye, Mexico, Iran, and Saudi Arabia. Node sizes indicate both countries' central role in global publication output and collaboration networks. The blue cluster consists mainly of European countries and others such as India, Brazil, and Israel. Germany, the UK, France, Italy, Sweden, and the Netherlands exhibit high centrality with dense and balanced connections, representing strong regional collaboration. Despite high internal connectivity, the blue cluster has comparatively weaker links with the central red cluster (USA–China).

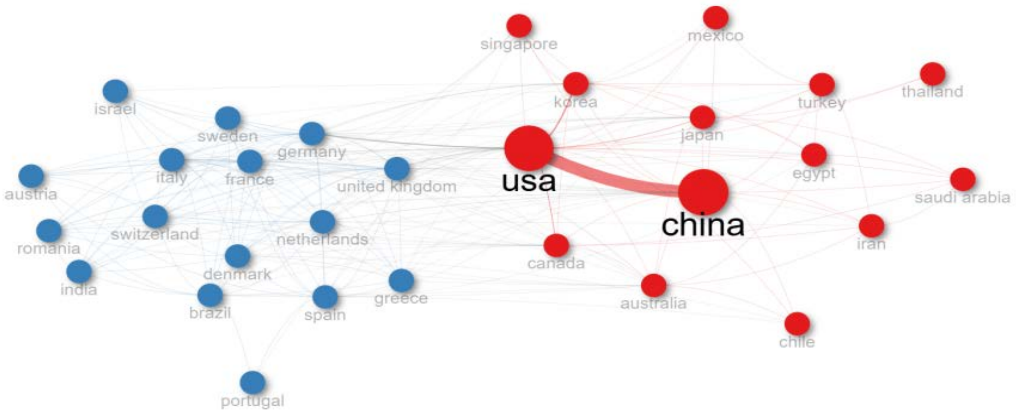


Figure 4c. Collaboration network analysis (Countries)

Overall, the network is characterized by high intra-cluster connectivity and clear leadership of cluster centers. Prominent collaborations between the USA and China suggest that a substantial portion of global publication output is concentrated along this axis, while the Europe-centered blue cluster demonstrates strong internal collaboration but relative detachment from the global network's main hubs.

Word and Thematic Analysis

Keyword analysis has become an essential tool in bibliometrics, enabling the identification of emerging research themes and providing insights for advancing HS research (22). Keyword co-occurrence networks and word clouds facilitate the detection of interrelated research areas and the temporal evolution of key terms (23).

Figure 5a. Word cloud from author's keywords

Figure 5a presents a word cloud illustrating the principal research foci and trends within the HS literature. The most frequent keywords include Hepatic Steatosis (1,124 occurrences), Non-Alcoholic Fatty Liver Disease – NAFLD (n=876), and Steatosis (n=339), indicating that research predominantly addresses non-alcoholic hepatic fat accumulation and general steatosis pathophysiology. Metabolic syndrome components such as Obesity (n=304), Fatty Liver (n=289), and Insulin Resistance (n=236) are also highly represented, highlighting the strong interplay between obesity, insulin resistance, and hepatic lipid accumulation. Pathophysiological mechanisms including Inflammation (n=137), Oxidative Stress (n=109), Lipid Metabolism (n=116), and Endoplasmic Reticulum Stress (n=75) emphasize the critical role of inflammatory and oxidative processes in disease progression.

Overall, the literature indicates that HS research primarily focuses on metabolic dysfunction, inflammation, oxidative stress, and fibrosis development, while non-invasive imaging methods and molecularly targeted therapeutic approaches are increasingly emphasized.

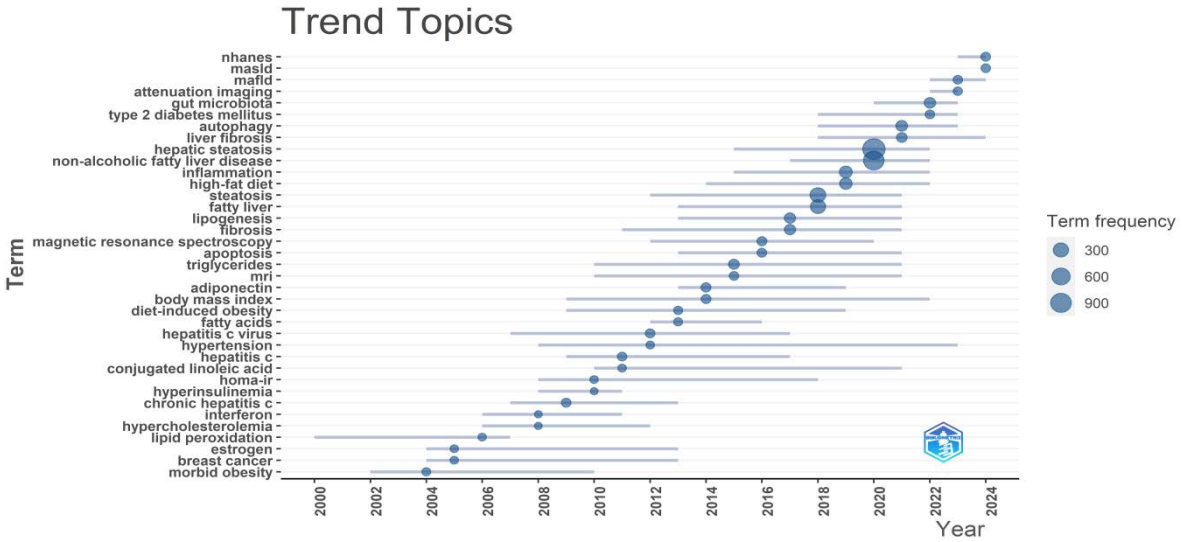


Figure 5b. Trend topics

Figure 5b visualizes the temporal evolution of keywords, showing which terms became prominent during specific years. Only keywords appearing at least five times per year are depicted. Line lengths indicate the duration of keyword usage, while node sizes represent usage frequency and relative prominence in the literature.

In the early 2000s, terms such as Morbid Obesity, Breast Cancer, Estrogen, Lipid Peroxidation, and

Hypercholesterolemia appeared with small nodes and short lines, indicating limited and transient research focus. Between 2005 and 2010, keywords including Interferon, Chronic Hepatitis C, Hyperinsulinemia, HOMA-IR, and Conjugated Linoleic Acid gained visibility but remained mostly confined to specific subfields. Post-2010, topics such as Hepatitis C, Hepatitis C Virus, Fatty Acids, Diet-Induced Obesity, Body Mass Index, and Adiponectin are represented with medium-sized nodes and longer lines, reflecting sustained and broader research interest. During this period, MRI and MRS emerged as increasingly used imaging modalities in HS research. From 2014 onward, keywords related to metabolic and pathophysiological processes-including Fibrosis, Lipogenesis, Fatty Liver, Steatosis, and High-Fat Diet-display long lines and medium-to-large nodes, indicating both consistent inclusion in the literature and high research volume. Inflammation, NAFLD, and HS show the largest nodes and longest lines, underscoring their status as core topics in the field.

In recent years (2020 onward), emerging trends include Autophagy, Type 2 Diabetes Mellitus, Gut Microbiota, Attenuation Imaging, MAFLD, MASLD, and NHANES. Notably, MAFLD and MASLD reflect rapid adoption of new diagnostic and classification frameworks, while Gut Microbiota and Type 2 Diabetes Mellitus highlight multidisciplinary research into systemic and microbiota-related aspects of HS.

In summary, the thematic evolution reveals a progression from early narrow and low-volume topics to metabolically, inflammatory, and imaging-focused studies post-2010, with recent emphasis on metabolic syndrome components, microbiota, and novel diagnostic approaches.

Figure 6 presents a thematic map of the HS literature generated using Bibliometrix. The map is based on 1,200 author keywords occurring at least five times, with topic clusters identified using the Louvain clustering algorithm. Each cluster is represented by its five most frequent keywords, and node sizes correspond to keyword frequency. Thematic maps are widely used bibliometric tools for examining the main topics and their interconnections within a research field. They effectively visualize the structure, interactions, and developmental trends of the literature (24).

Clusters are categorized along centrality and density axes into four types. Motor themes possess both high centrality and high density, representing foundational topics that drive field development. Niche themes have high density but low centrality, indicating specialized and well-developed subtopics. Emerging or declining themes display low centrality and low density, representing topics either losing relevance or still underdeveloped. Basic themes exhibit high centrality but low density, marking concepts central to the field yet not fully matured (25).

Motor themes, characterized by high centrality and density, guide the development of HS research. The green cluster-Steatosis, Liver, Liver Steatosis, Fibrosis, Controlled Attenuation Parameter-represents current core topics focused on hepatic fat accumulation and fibrosis assessment. The orange cluster-AMP-Activated Protein Kinase, Autophagy, Endoplasmic Reticulum Stress, Adiponectin, PPAR Alpha-captures molecular mechanisms critical to understanding the cellular and biochemical pathophysiology of HS.

Niche themes show high density within their subdomains but limited overall centrality. The gray cluster (Metabolism) reflects studies investigating detailed metabolic processes, while the pink cluster (Fructose) highlights research focused on fructose's role in metabolism and hepatic fat accumulation, representing specialized subfield interests.

Emerging or declining themes, with low centrality and density, indicate either waning or still-developing topics. The purple cluster Fatty Liver, MRI, Ultrasonography, CT, MRS represents imaging methods that were historically important in HS diagnosis but are increasingly replaced by newer diagnostic approaches. The brown cluster Triglycerides, Cholesterol reflects classic metabolic parameters that, while informative, show relatively declining focus.

Basic themes, with high centrality but lower density, form the conceptual backbone of HS research. The blue cluster NAFLD, Lipid Metabolism, Metabolic Syndrome, NASH, Liver Fibrosis defines the clinical and metabolic framework of HS. The red cluster HS, Obesity, Insulin Resistance, Inflammation, High-Fat Diet focuses on pathogenesis, risk factors, and nutritional associations.

Overall, the thematic map indicates that many future research opportunities lie within the basic themes quadrant. High centrality values identify these topics as central to the field, while lower density levels suggest potential for further development. Specifically, NAFLD, Lipid Metabolism, Metabolic Syndrome, NASH, and Liver Fibrosis (blue cluster) are crucial for understanding HS's clinical features, metabolic aspects, and progression. HS, Obesity, Insulin Resistance, Inflammation, and High-Fat Diet (red cluster) represent fundamental areas for investigating pathogenesis, lifestyle factors, and metabolic dysfunction. These themes are likely to guide future

studies on molecular mechanisms, non-invasive diagnostic tools, and targeted therapeutic strategies in HS research.

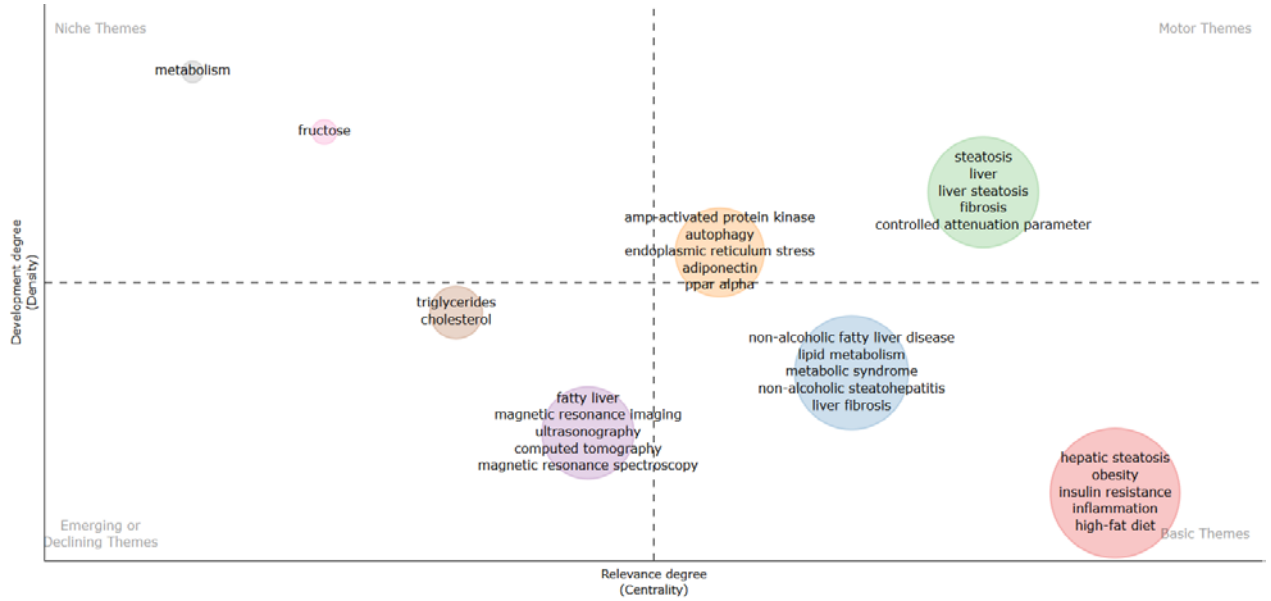


Figure 6. Thematic map

Discussion

The aim of this study was to conduct a bibliometric analysis of HS-related publications indexed in the WoS database over the past 45 years, identifying global research trends, leading authors, institutions, and countries, as well as influential journals and potential future research directions.

The analyzed data reveal that research on HS has experienced rapid growth over the last 45 years. A total of 3,871 articles were produced by 20,911 authors, with single-author publications being relatively rare, indicating that research in this field is largely collaborative and team-oriented. High citation counts and an average publication age of 8.3 years suggest that the literature is both well-established and continually updated in line with current developments. The international collaboration rate exceeding 20% highlights the global significance of HS research and contributions from multiple countries. Additionally, the annual growth rate and high average citation impact indicate increasing interest in the field and the strong influence of this knowledge on the scientific community.

In terms of influential journals publishing on HS, Hepatology, the official journal of the American Association for the Study of Liver Diseases, ranks first; Journal of Hepatology, the official journal of the European Association for the Study of the Liver, ranks second; and Plos One, an independent platform of the Public Library of Science, ranks third.

Regarding the most cited articles, the top publication is Browning et al.'s 2004 study in Hepatology titled "Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity". This research examined liver triglyceride content across a multi-ethnic population, evaluating differences by ethnicity and sex. The study found that HS prevalence was higher in Hispanic individuals and white males compared to other ethnic groups and white females, suggesting that ethnicity and sex may influence steatosis-associated liver disease risk (26).

The second most cited study, also from 2004, by Browning and Horton in J Clin Invest, titled "Molecular mediators of hepatic steatosis and liver injury", investigated the molecular mechanisms underlying obesity-related HS and non-alcoholic steatohepatitis. The findings highlighted that HS can follow a benign course in some cases, whereas steatohepatitis may progress to end-stage liver disease and account for 14% of liver transplants in the USA. Understanding these molecular mechanisms is crucial for advancing disease management and therapeutic strategies (27).

The third most influential study is Szczepaniak et al.'s 2005 publication in Am J Physiol Endocrinol Metab, titled "Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population". This study quantitatively measured hepatic triglyceride content (HTGC) using proton magnetic resonance spectroscopy (MRS) in the Dallas Heart Study cohort, determining a normal upper limit and estimating HS prevalence. MRS proved to be a reliable, non-invasive method for HTGC assessment, revealing a

high HS prevalence (33.6%) in a large US population (28).

Bibliometric analyses also identified the most productive and impactful researchers in HS. Prof. Yu Li (Shanghai Institute for Nutrition and Health, Chinese Academy of Sciences, Metabolic Disease Research Division, China) emerged as the leading author, with both high publication output and citation impact. He is followed by Prof. Yuxiu Liu (Department of Hepatology, Hepatology Research Institute, The First Affiliated Hospital, Fujian Medical University, China), known for contributions to liver disease and metabolic disorders, and Asst. Prof. Hyunbae Kim (Center for Molecular Medicine and Genetics, Wayne State University, USA), recognized for translational research. These findings indicate that research leadership in HS is predominantly centered in China, with notable contributions from the USA. Prior bibliometric studies also report China's rapid increase not only in publication volume but also in highly cited authors, highlighting the pivotal role of regional research strategies in shaping global scientific leadership (29,30).

When evaluating countries based on publication output in HS, China, the USA, and South Korea are prominent. This suggests increasing investment by Asian countries in research on metabolic diseases, obesity, and liver disorders in recent years (31,32). Our findings show that scientific contributions in HS are mainly concentrated in Asia, North America, and Western Europe, while countries from South America and the Middle East are increasingly participating. Similar trends have been reported in recent bibliometric analyses on liver disease and metabolic syndrome, emphasizing Asia's significant rise in scientific output, likely driven by regional epidemiological burdens and investment in research infrastructure (33,34).

Collaboration network analyses provide insights into the relationships among authors, institutions, and countries in HS research, allowing a better understanding of the social structure of scientific production (19,20). Our analyses indicate that author clusters centered around Li Y and Zhang Y, as well as groups led by Kim H, Li J, and Wang J, maintain strong connections both internally and with other clusters. These findings suggest that HS research is largely team-based and internationally collaborative, consistent with reports from other hepatology studies (35).

Institutional collaboration analyses highlight the central roles of the University of California System, Harvard University, and Yonsei University. These institutions enhance scientific productivity and impact through strategic regional and international collaborations. The high productivity of China- and US-based institutions in their respective regions indicates a persistent core–periphery structure within the global scientific network (21).

Country-level collaboration analyses emphasize the central role of the USA and China in global research output. Although Europe-centered clusters maintain strong regional collaborations, their connections to global leaders are comparatively limited. This observation reflects the existence of international asymmetries in HS research and underscores the importance of regional research strategies in shaping scientific leadership (36).

Overall, collaboration network analyses demonstrate that HS research is not only defined by productivity but also by the impact of scientific influence and the dynamics of collaboration. These findings are valuable for identifying leading authors and institutions, guiding future strategic collaborations, and informing global research policy planning.

Keyword and thematic map analyses reveal increasing research focus on metabolic, inflammatory, and diagnostic aspects of HS. The most frequent terms-HS, NAFLD, obesity, insulin resistance, and inflammation-confirm the central role of obesity and metabolic syndrome components in disease pathogenesis. The prominence of molecular keywords such as AMP-Activated Protein Kinase, Autophagy, PPAR Alpha, and Adiponectin underscores the importance of understanding cellular mechanisms and developing targeted therapies (37). The thematic map results indicate that basic themes with high centrality but low-to-moderate density form the main research axes, with substantial potential for further development. These findings point to a continuing multidisciplinary trend, emphasizing emerging research areas such as metabolic syndrome, gut microbiota, and non-invasive diagnostic methods as future priorities.

Study limitations

However, the study has several limitations that may introduce systematic bias. First, only publications indexed in the WoS were included, potentially overlooking relevant articles in other databases such as Scopus, PubMed, or regional repositories, which may lead to an incomplete representation of global research activity. Second, only English-language publications were considered, possibly underrepresenting contributions from non-English-speaking countries and regions, thus introducing a language-related selection bias. Third, bibliometric indicators such as publication counts and citation metrics provide quantitative measures of research output but do not directly assess the scientific quality, clinical relevance, or methodological rigor of individual studies, which may

bias the perceived impact of the research field. Finally, variations in terminology (e.g., HS, NAFLD, MAFLD, MASLD) and keyword selection may result in the omission of relevant studies, further contributing to potential systematic bias. Future studies integrating multiple databases, diverse citation analysis methods, and multidisciplinary evaluations could provide a more comprehensive global perspective on HS research.

Conclusions

This bibliometric analysis comprehensively illustrates the global development of HS research from 1980 to 2025, including leading authors, institutions, journals, and thematic trends. The 3,871 analyzed articles and 20,911 authors demonstrate a rapid increase in collaborative, internationally oriented research over the last 45 years. Leading researchers such as Prof. Yu Li, Prof. Yuxiu Liu, and Asst. Prof. Hyunbae Kim maintain influence through high publication output and citation impact. Journals including Hepatology, Journal of Hepatology, and PLOS One represent the most influential publication platforms in HS research. Keyword and thematic analyses indicate growing interest in metabolic syndrome, inflammation, non-invasive diagnostics, and molecular mechanisms (AMPK, autophagy, PPAR alpha, adiponectin), highlighting the multidisciplinary progression of HS research encompassing both pathophysiological and clinical aspects. Future studies integrating multiple databases, broader linguistic inclusion, diverse citation analysis methods, and multidisciplinary evaluations could mitigate biases and provide a more comprehensive and balanced global perspective on HS research.

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Data Availability: *The data used to support the findings of this study are available from the corresponding author upon request*
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Case Report

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Silicone Frontal Suspension Surgery in a 3-month-old Infant with Unilateral Congenital Ptosis: Case Report

Unilateral Konjenital Pitozu Olan 3 Aylık Bebekte Silikon Frontal Askı Ameliyatı: Vaka Sunumu

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Abstract

This case report discusses the outcomes of a silicone frontalis sling surgery performed on a 3-month-old female infant diagnosed with congenital ptosis of the left eye. Congenital ptosis, characterized by drooping of the upper eyelid present at birth, can lead to amblyopia, strabismus, and other visual impairments if not treated promptly. In cases where levator function is inadequate, frontalis suspension surgery is considered the gold standard treatment for congenital ptosis. This case presents a patient who underwent early intervention with a silicone frontalis sling technique.

Keywords: Congenital Ptosis, Silicone Frontalis Sling, Eyelid Drooping, Surgical Outcomes

ÖZ

Bu vaka sunumunda, sol göz konjenital pitozu tanısı almış 3 aylık bir kız bebekte uygulanan silikon frontal askı ameliyatının sonuçları tartışılmaktadır. Konjenital pitoz, doğumsal bir göz kapağı düşüklüğü olup erken tedavi edilmediğinde ambliyopi, strabismus ve diğer görsel sorunlar gelişebilir. Konjenital pitoz tedavisinde frontal askı cerrahisi, levator fonksiyonunun yetersiz olduğu olgularda altın standart tedavi yöntemidir. Bu vaka, erken dönemde silikon frontal askı yöntemiyle tedavi edilen bir hastayı içermektedir.

Anahtar kelimeler: Konjenital Pitoz, Silikon Frontal Askı, Göz Kapağı Düşüklüğü, Ameliyat

Highlights

- Early silicone frontalis sling surgery at 3 months successfully prevented stimulus-deprivation amblyopia in severe congenital ptosis.
- FOX pentagon technique achieved excellent functional outcomes (MRD1: 3mm) with minimal complications in an infant patient.
- Silicone material offers practical advantages over autogenous fascia lata in early pediatric ptosis surgery.

Introduction

Congenital ptosis presents at birth or within the first year of life. It may affect one or both eyes and can vary in severity. The condition is associated with dysgenesis of the levator muscle or defects in neuronal migration, leading to a loss of muscle elasticity. If not treated early, congenital ptosis can result in amblyopia, strabismus, and other visual impairments (1). In cases where there is a risk of amblyopia, early surgical intervention should be considered. If no such risk is present, surgery may be postponed until around 3–4 years of age to allow for a more accurate assessment of levator muscle function. Frontalis sling surgery is considered the gold standard treatment for cases with poor levator function (2). This case represents a situation where early surgical intervention and subsequent follow-up were successfully managed.

Case Presentation

Informed consent was obtained from the patient's parent/legal guardian for publication of this case report.

A 3-month-old female infant was referred to our clinic due to drooping of the left upper eyelid. The patient's birth history revealed that she was born at 39 weeks of gestation via normal vaginal delivery, weighing 3300 grams. There were no systemic, congenital, or genetic diseases reported, and no family history of ptosis was identified. Preoperative examination showed unrestricted bilateral ocular motility in all directions, normal anterior chamber structures, and a clear cornea. Fundus examination was unremarkable. Pupillary light reflexes were positive for both direct and consensual responses. Levator muscle function in the left eye was measured by asking the patient to look down and then up while manually immobilizing the frontalis muscle, measuring the excursion of the upper eyelid margin, which was found to be 2-3 mm (normal >15 mm).

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The margin reflex distance (MRD1) was measured as the distance between the upper eyelid margin and the corneal light reflex in primary gaze position, which was 1 mm (normal 4-5 mm). Bell's phenomenon was found to be positive. Schirmer testing could not be reliably performed **(Figure 1)**.

Figure 1. Initial presentation showing ptosis of the patient

Visual assessment in this 3-month-old infant was performed using age-appropriate methods including fixation behavior assessment, pupillary light reflexes, and observation of visual tracking responses. While formal visual acuity testing is not feasible at this age, the presence of complete ptosis with pupil occlusion posed a significant risk for stimulus-deprivation amblyopia, necessitating immediate surgical intervention.

Given the risk of amblyopia in the left eye, early surgical intervention was deemed necessary. Silicone frontalis sling surgery was planned for the patient. Detailed informed consent was obtained from the patient's legal guardian

The surgical procedure was performed under general anesthesia using a silicone sling material according to the FOX pentagon technique. The FOX pentagon technique involves creating a pentagonal configuration with the silicone sling material (3)(**Figure 2)**.

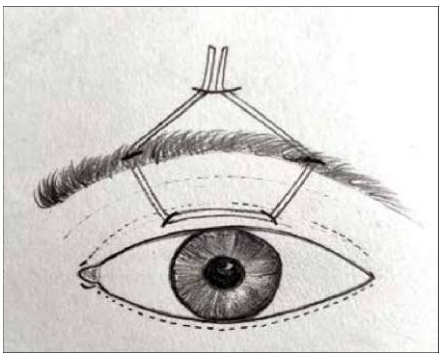

Figure 2. Illustrative figure demonstrating the FOX pentagon technique

The sling passes through two eyelid incisions (positioned 1mm medial to the medial limbus and 1mm lateral to the lateral limbus) and three forehead incisions (positioned above the medial, central, and lateral aspects of the eyebrow). The silicone material forms a pentagon shape, with the base along the eyelid margin and the apex at the central forehead incision (4). Two small incisions were made just 1–2 mm above the lash line, positioned 1 mm medial to the medial limbus and 1 mm lateral to the lateral limbus. Three brow incisions were also made on the forehead. The silicone sling material was passed through the eyelid incisions with the aid of a Wright needle, forming a pentagonal configuration. The eyelid was adjusted to align with the superior limbus. Incision sites were closed with 6-0 Vicryl sutures, and the eye was tightly patched postoperatively.

The surgical procedure was completed without complications. On the first postoperative day **(Figure 3)** and at the 10-day follow-up **(Figure 4)**, the eyelid was observed to be in a normal position, with an MRD1 of 3 mm. A 1

mm degree of lagophthalmos was noted on the first postoperative day. Written informed consent was obtained from the parents for the case report and publication of the photographs.

Figure 3. Postoperative appearance of the patient on day 1.

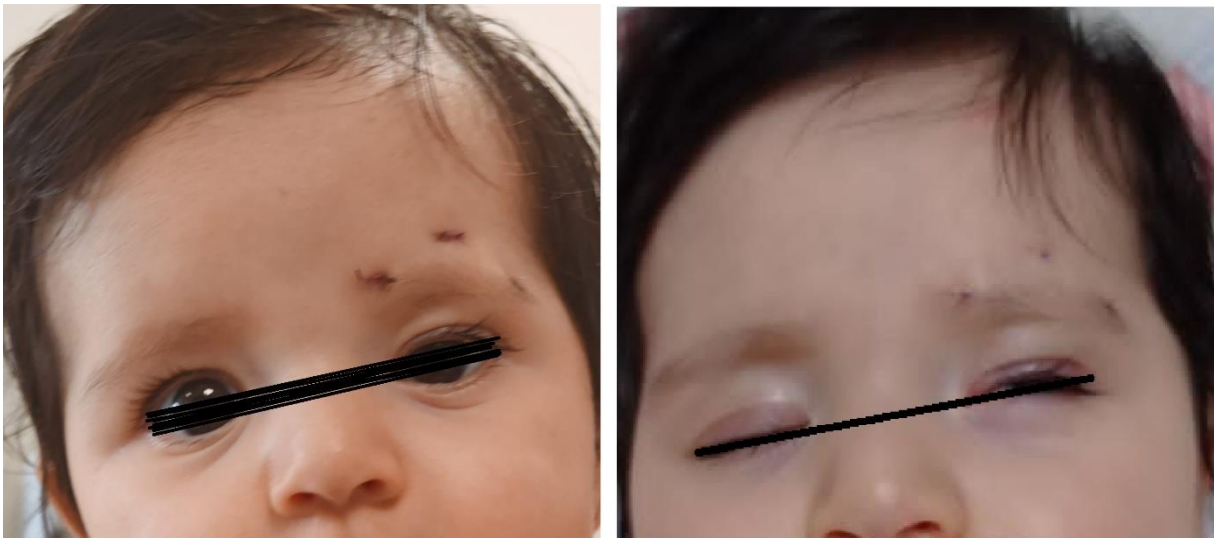

Figure 4. Postoperative appearance of the patient on day 10.

Discussion

In patients with congenital ptosis, early surgical intervention is crucial when there is a risk of amblyopia. Frontalis sling surgery is the most commonly used surgical technique for patients with poor levator muscle function and moderate to severe ptosis. In this procedure, the tarsus is suspended from the frontalis muscle using materials that can be autogenous, allogenic, or synthetic. Elevation of the eyebrows results in the lifting of the upper eyelids (5). Although autogenous fascia lata is considered the gold standard material for frontalis suspension in congenital ptosis treatment, harvesting fascia lata from infants can be challenging. Additionally, the need for an extra surgical site, which may not be accepted by parents, and the possibility of permanent thigh scarring are significant disadvantages. Synthetic materials are more readily available and can shorten surgical time; however, they carry higher risks of complications such as infection, rejection, and granuloma formation (6). Recent studies by Ghiam et al. (2023) and Thacker et al. (2025) have shown similar success rates with silicone slings compared to other synthetic materials, with lower infection rates and easier revision surgery when needed (7,8). Comparative analysis of different surgical approaches demonstrates that frontalis sling surgery in infants under 6 months shows excellent functional outcomes with minimal complications when performed by experienced surgeons. The silicone material offers advantages including biocompatibility, ease of handling, and the ability to adjust tension postoperatively if needed.

The observed 1 mm lagophthalmos is considered mild and typically well-tolerated in pediatric patients. However, long-term monitoring for dry eye symptoms is essential. Postoperative care should include artificial tear supplementation and regular assessment of corneal integrity. In our case, no signs of corneal desiccation were observed during the follow-up period, and Bell's phenomenon was preserved, providing additional protection
In this case, early application of a silicone frontalis sling surgery resulted in successful outcomes without any complications.

Study Limitations

This case report has several limitations. The short follow-up period (10 days) prevents assessment of long-term outcomes and potential complications. As a single case, findings cannot be generalized to all pediatric ptosis patients. Additionally, comprehensive visual acuity and Schirmer testing could not be performed due to the patient's young age (3 months). Long-term follow-up is necessary to evaluate surgical durability and late complications.

Conclusion

Congenital ptosis, if left untreated during infancy, can negatively impact visual development. This case highlights that silicone frontalis sling surgery is an effective and safe treatment option even at a young age in patients with congenital ptosis, and that early intervention can lead to successful outcomes.

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Review

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Current Approaches in Cupping Therapy

Kupa Terapide Güncel Yaklaşımlar

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Abstract

Cupping therapy is a traditional treatment method with deep historical roots in Ancient Egyptian Medicine, Traditional Chinese Medicine, and Islamic medicine. Its techniques include dry, wet, and moving cupping. Its proposed mechanism of action involves creating negative pressure and enhancing blood flow, thereby reducing inflammation, triggering endogenous pain modulation, and supporting immune functions. From the perspective of Traditional Chinese Medicine, it regulates the flow of energy, while in Islamic medicine, it is suggested to facilitate the removal of toxins. Recent studies have demonstrated that cupping therapy is effective in managing musculoskeletal pain, rheumatic conditions, sports rehabilitation, and circulatory health. It has been reported to alleviate pain and improve quality of life in conditions such as chronic low back pain, fibromyalgia, knee osteoarthritis, and plantar fasciitis. Furthermore, beneficial effects in neurological and psychological disorders such as migraine and depression have been documented, showing an improvement in symptoms, reduced stress, and better anxiety management. In the context of sports injuries and post-exercise muscle pain, cupping therapy accelerates recovery and increases endurance. Additionally, it has been reported to help control symptoms in asthma and enhance patient satisfaction. In abdominal obesity and metabolic syndrome, cupping therapy reduces waist circumference and triglyceride levels, yielding results comparable to acupuncture. In conclusion, cupping therapy stands out as a complementary method in various healthcare fields. However, methodological limitations in current research necessitate further studies to verify its efficacy and safety. Standardized protocols and objective measurements will bolster the scientific evidence supporting this treatment.

Keywords: Cupping therapy, Current Approach, Traditional treatment

ÖZ

Amaç: Kupa terapisi, Antik Mısır Tıbbı, Geleneksel Çin Tıbbı ve İslam tıbbında derin tarihi kökleri olan geleneksel bir tedavi yöntemidir. Teknikleri arasında kuru, yaş ve hareketli kupa yer alır. Önerilen etki mekanizması, negatif basınç oluşturarak kan akışını artırmayı, böylece iltihabı azaltmayı, endojen ağrı modülasyonunu tetiklemeyi ve bağışıklık fonksiyonlarını desteklemeyi içerir. Geleneksel Çin Tıbbı perspektifinden bakıldığında, enerji akışını düzenlediği, İslam tıbbında ise toksinlerin vücuttan atılmasını kolaylaştırdığı önerilmektedir.

Son çalışmalar, kupa terapisinin kas-iskelet ağrıları, romatizmal rahatsızlıklar, spor rehabilitasyonu ve dolaşım sağlığı yönetiminde etkili olduğunu göstermiştir. Kronik bel ağrısı, fibromiyalji, diz osteoartriti ve plantar fasiit gibi durumlarda ağrıyı hafifletip yaşam kalitesini artırdığı bildirilmiştir. Ayrıca migren ve depresyon gibi nörolojik ve psikolojik rahatsızlıklarda belirtilerin iyileştiği, stresin azaldığı ve anksiyete yönetiminin desteklendiği rapor edilmiştir. Spor yaralanmaları ve egzersiz sonrası kas ağrısı bağlamında ise, kupa terapisinin iyileşmeyi hızlandırdığı ve dayanıklılığı artırdığı belirtilmiştir.

Ek olarak, astım semptomlarının kontrolünde ve hasta memnuniyetinin artırılmasında faydalı olduğu rapor edilmiştir. Abdominal obezite ve metabolik sendrom durumlarında, kupa terapisinin bel çevresini ve trigliserit seviyelerini azalttığı ve bu sonuçların akupunktura benzer olduğu görülmüştür.

Sonuç olarak, kupa terapisi çeşitli sağlık alanlarında tamamlayıcı bir yöntem olarak öne çıkmaktadır. Ancak, mevcut araştırmalardaki metodolojik sınırlamalar, etkinliğinin ve güvenliğinin doğrulanması için daha fazla çalışmayı gerekli kılmaktadır. Standart protokoller ve objektif ölçümler, bu tedavi yöntemini destekleyen bilimsel kanıtları güçlendirecektir.

Anahtar kelimeler: Kupa terapisi, Güncel yaklaşım, Geleneksel tedavi

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Highlights

- Cupping therapy helps with pain, rheumatic conditions, sports recovery, and mental health issues like migraines and depression.
- It reduces waist size, triglycerides, and aids asthma symptom control.
- Despite its diverse applications, methodological limitations in current studies highlight the need for standardized protocols and objective measurements to validate its efficacy and safety.

Introduction

Cupping therapy is a modality within traditional medicine that has spanned from antiquity to the present day. Historical data show that this therapy technique has held an important place in the medical literature of Ancient Egypt, Traditional Chinese Medicine, and Islamic medicine (particularly in the form referred to as "hijama") (1–3). When examining the methods and mechanisms of cupping therapy, it is evident that various techniques—including dry cupping, wet cupping, and moving cupping—are employed (2,4). The mechanism of action is believed to involve the generation of negative pressure and enhanced circulation, increasing regional blood and lymph flow, and thus delivering more oxygen and nutrients to the tissues. Additionally, it may modulate inflammatory responses and pain by inducing mild stimulation on the skin that activates endogenous pain modulation mechanisms, triggering the release of certain cytokines and neuropeptides that reduce inflammation. In Traditional Chinese Medicine, cupping therapy is thought to balance energy (qi) flow by focusing on meridians and acupuncture points, while in Islamic medicine ("hijama"), it is proposed to support the body's detoxification processes, boost blood circulation, and reinforce immune function (2–4). With roots dating back thousands of years, cupping therapy appears in written sources in both Far Eastern and Middle Eastern medicine in various forms (3). Modern scientific research has increasingly focused on its potential benefits in a wide range of areas, particularly pain control, musculoskeletal conditions, and enhancing circulation (1,4).

Literature Review Method

This review was compiled by searching international databases such as PubMed, Scopus, Web of Science, and Google Scholar between 2019 and 2023 using the keywords "cupping therapy," "kupa terapisi," "hijama," and "complementary and alternative medicine." Inclusion criteria encompass peer-reviewed clinical studies, meta-analyses, and systematic reviews published between 2019 and 2023 focusing on cupping therapy's efficacy in various conditions, while exclusion criteria include non-clinical studies, case reports, and publications with insufficient methodological rigor. A total of 65 studies were reviewed, including 40 clinical trials, 15 meta-analyses, and 10 systematic reviews.

Studies identified as relevant based on title and abstract screening were accessed in full text, with a primary focus on clinical research and meta-analyses. The objective of this extensive literature search was to identify current trends and potential research gaps regarding cupping therapy in recent literature. The following section provides a multifaceted evaluation of the theoretical foundations and clinical efficacy of cupping therapy. It discusses the main themes, case selection criteria, intervention methods, and reported outcomes of the selected studies.

Musculoskeletal Pain and Rheumatic Diseases

Cupping therapy has been described as a method offering remarkable effects in the management of musculoskeletal pain and rheumatic diseases. Studies on chronic low back pain have reported that dry cupping alleviates pain and improves quality of life. When applied in conjunction with Traditional Chinese Medicine approaches, cupping therapy has shown a more pronounced effect compared to nonsteroidal anti-inflammatory drugs (5). Similarly, dry cupping has been reported to significantly reduce pain levels in nonspecific neck pain in the short term, providing quicker pain relief when combined with ischemic compression of trigger points (6). In patients with fibromyalgia, wet cupping has proven effective in relieving pain and sleep disturbances, leading to a meaningful reduction in both pain intensity and the number of tender points. These outcomes suggest that cupping therapy may serve as a complementary option for fibromyalgia management (7).

In patients with knee osteoarthritis, cupping therapy has been reported to reduce pain and stiffness while contributing to functional improvement; meta-analyses underscore its significance in enhancing physical function and mitigating symptoms (8). Moreover, in cases of plantar fasciitis, dry cupping was found effective in relieving heel pain and facilitating functional recovery, with marked improvement in pain severity and range of motion (9).

Collectively, these findings suggest that cupping therapy may be a promising complementary method for pain management and quality-of-life enhancement in musculoskeletal and rheumatic conditions. The improved blood flow and reduced inflammatory markers observed with cupping therapy directly correspond to the reduction in pain and stiffness reported in conditions like knee osteoarthritis. Beyond physical pain, cupping therapy has shown promise in addressing conditions with a neurological and psychological basis, further broadening its therapeutic scope.

Neurological and Psychological Disorders

Cupping therapy is also viewed as a method with potential benefits for neurological and psychological disorders. For example, wet cupping has been reported to reduce the frequency and intensity of migraine attacks, with one study noting an average 66% decrease in headache severity. Moreover, the reported side effects were mild and transient (10). It has additionally been proposed that the regulatory effects of cupping therapy on circulation may aid stress and anxiety management. In the treatment of depressive disorders, a combination of acupuncture, cupping therapy, and physical exercise has shown favorable results by promoting overall mental and physical well-being (11). The regulation of blood flow and reduction in neuroinflammatory markers may underlie the observed decrease in migraine severity and improved anxiety management.

Sports Health and Rehabilitation

Cupping therapy has also garnered attention as an auxiliary method for sports injuries and post-exercise muscle soreness. Dry and moving cupping applications reportedly expedite muscle recovery processes by reducing post-exercise pain, and they further increase muscle strength and endurance (12). For sports injuries, it is suggested that cupping therapy promotes healing by regulating circulation and diminishing inflammation. Studies in this area have demonstrated lower perceived pain levels and enhanced joint mobility (13). The benefits of cupping therapy on physical recovery and performance extend to cardiovascular and circulatory health, highlighting its systemic effects.

Circulatory and Cardiovascular Health

Cupping therapy may have cardioprotective benefits, as it has been associated with improvements in electrocardiographic parameters, possibly playing a role in arrhythmia management. Certain research indicates that dry cupping significantly reduces arrhythmia prevalence (14). Additionally, using larger-sized cups has been reported to enhance cutaneous blood flow more effectively, potentially strengthening the circulatory benefits of the method (15).

Dermatological Conditions

Cupping therapy has also shown promise as a complementary approach for dermatological disorders. Moving cupping in plaque psoriasis has been observed to reduce both inflammation and skin thickening, yielding significant improvements in PASI and DLQI scores; no relapse was reported during a six-month follow-up (16). For eczema, wet cupping has demonstrated symptomatic relief, although larger scale randomized controlled trials are needed for more conclusive evidence.

Respiratory Disorders

In asthma, wet cupping therapy may prove effective in symptom management and improving patient satisfaction. Studies have reported notable improvements in asthma control scores and a significant increase in patient satisfaction with treatment (17).

Obesity and Metabolic Diseases

For abdominal obesity and metabolic syndrome, medical cupping therapy has been shown to reduce waist circumference, triglyceride levels, and subcutaneous fat thickness, providing results comparable to acupuncture. Moreover, the lower frequency of treatment sessions compared to some other interventions is considered an advantage that may enhance patient compliance (18–20).

Clinical Applications of Cupping Therapy

Cupping therapy has been applied in various clinical settings, demonstrating benefits across multiple conditions. For musculoskeletal pain, such as chronic low back pain and knee osteoarthritis, it has been shown to reduce pain intensity and improve physical function (5, 8). In fibromyalgia, it alleviates pain and sleep disturbances by decreasing the number of tender points (7). Neurological disorders like migraines have also been addressed, with studies reporting reduced headache frequency and severity (10). In respiratory conditions, wet cupping has been linked to improved asthma control and higher patient satisfaction (17). Additionally, cupping therapy has been explored for its role in reducing waist circumference and triglyceride levels in patients with abdominal obesity and metabolic syndrome, showing results comparable to acupuncture (18–20). Additionally, promising results have been obtained in epileptic patients (21,22).

These findings underline cupping therapy's versatility as a complementary approach, although further studies are needed to validate its effects in larger populations.

Recommendations and Conclusions

Studies from 2019 to 2023 indicate that cupping therapy may serve as a supportive method for a range of conditions, notably musculoskeletal pain, certain chronic pain syndromes, sports rehabilitation, and circulatory disorders. Despite a recent surge in research on cupping therapy, methodological limitations and the absence of standardized treatment protocols make it difficult to generalize findings. Therefore, more advanced research designs, including the use of blinding and appropriate control groups, are needed to strengthen the foundational evidence of its efficacy and safety. Future investigations are expected to integrate comprehensive and long-term clinical trials with standardized cupping protocols, controlled and blinded methodologies, and objective measurements of biological markers (e.g., inflammation, tissue oxygenation). This approach will help establish a robust scientific foundation on the efficacy, safety, and applicability of cupping therapy.

To advance the understanding and application of cupping therapy, future research should focus on developing standardized protocols that include parameters such as cup size, duration, and frequency. Additionally, exploring the effects of cupping therapy on biomarkers related to inflammation, tissue oxygenation, and immune function could provide valuable insights into its mechanisms of action. Conducting long-term randomized controlled trials is also essential to comprehensively evaluate its efficacy and safety across diverse patient populations.

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