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CONTENTS

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CONTENTS

Analysis of Brain Activation and Effective Connectivity During Self-paced Unilateral and Bilateral Finger Tapping Using Functional Magnetic Resonance Imaging in Patients with Temporal Lobe Epilepsy

Temporal Lob Epilepsisi Hastalarında Fonksiyonel Manyetik Rezonans Görüntüleme Kullanarak Öznel Zamanlı Tek Taraflı ve Çift Taraflı Parmak Tıklama Sırasında Beyin Aktivasyonu ve Etkin Bağlantılılığın Analizi

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ABSTRACT

Objective: The temporal lobes are the most frequent sites of origin of partial seizures. Patients with temporal lobe epilepsy (TLE) represent approximately two thirds of the intractable seizure population. This study aims to explore motor networks in TLE patients.

Methods: This study involves 12 healthy subjects and 12 TLE patients who have undergone functional magnetic resonance imaging performing self-paced unilateral and bilateral finger tapping. The images were then preprocessed and analyzed using statistical parametric mapping. The activated areas were compared between healthy subjects and TLE patients. The effective connectivity for visual and motor nodes was performed using dynamic causal modelling.

Results: Comparing the two groups, using two samples t-test, familywise error rate p<0.05. Healthy subjects showed more areas of significant activation. For effective connectivity, in healthy subjects, visual to motor was the dominant model with average value of 0.03 Hz, bilaterally. In TLE patients, on the right hemisphere, a contrary result was observed whereby the motor to visual area was the dominant

ÖZ

Amaç: Temporal lob, kısmi nöbetlerin en sık başlangıç noktasıdır. Temporal lob epilepsisi (TLE) olan hastalar, kontrol edilemeyen nöbet popülasyonunun yaklaşık üçte ikisini temsil eder. Bu çalışma, TLE hastalarında motor ağları incelemeyi amaçlamaktadır.

Yöntemler: Bu çalışma, kendi hızında tek taraflı ve çift taraflı parmak tıklama gerçekleştiren fonksiyonel manyetik rezonans görüntüleme uygulanan 12 sağlıklı denek ve 12 TLE hastasını içermektedir. Görüntüler daha sonra ön işlemden geçirilmiş ve istatistiksel parametrik Haritalama kullanılarak analiz edilmiştir. Aktive olan alanlar sağlıklı deneklerle TLE hastaları arasında karşılaştırılmıştır. Görsel ve motor düğümleri arasındaki etkin bağlantı dinamik nedensel modelle kullanılarak analiz edilmiştir.

Bulgular: İki grubun karşılaştırılması sonucunda, iki örnek t-testi, aile düzeyinde hata oranı p<0,05 ile sağlıklı deneklerde daha fazla anlamlı aktivasyon alanı gözlemlenmiştir. Etkin bağlantıda, sağlıklı deneklerde görselden motor alana doğru model baskındı ve çift taraflı olarak ortalama değer 0,03 Hz idi. TLE hastalarında, sağ yarımkürede motor alandan görsel alana doğru ters bir sonuç gözlemlenmiştir, yani bu

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Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

ABSTRACT

pattern. On the left hemisphere, the model was the same as in healthy subjects, visual to motor, but with a higher average value of 0.1 Hz.

Conclusion: This study found that there were fewer areas of the brain with significant activation in TLE patients during motor activity. TLE brains also exhibit alteration in effective connectivity between visual and motor regions.

Keywords: Temporal lobe epilepsy, functional magnetic resonance imaging, finger tapping

ÖZ

model baskındı. Sol yarımkürede, sağlıklı deneklerde olduğu gibi görselden motor alana doğru model baskındı, ancak ortalama değer 0,1 Hz ile daha yüksekti.

Sonuç: Bu çalışma, TLE hastalarında motor aktivite sırasında anlamlı aktivasyon gösteren beyin alanlarının daha az olduğunu bulmuştur. TLE beyinleri ayrıca görsel ve motor bölgeler arasındaki etkin bağlantıda değişiklikler göstermektedir.

Anahtar Sözcükler: Temporal lob epilepsisi, fonksiyonel manyetik rezonans görüntüleme, parmak vurma

INTRODUCTION

Epilepsy is a disorder of the central nervous system that is characterized by recurrent seizures unprovoked by acute systemic or neurological insult. Seizures are a clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. It is a condition where a sequence of events turns a normal neuronal network into a hyperexcitable network (1). Temporal lobe is the most frequent site of origin of partial seizures. Patients with temporal lobe epilepsy (TLE) represent approximately two thirds of the intractable seizure population, which may require surgical management (2).

TLE can be conceptualized as a network disease. The network can be characterized by inter-regional functional connectivity, i.e., correlations between any two regions (3). Traditionally, TLE has been known to cause memory and language impairment (4). However, studies have also shown that there was clinical evidence of motor dysfunction as well in patients with focal epilepsy (5-8), which necessitates further study on the motor network. With the development of neuroimaging, it is possible to study nervous system diseases at the network level. The in-depth study of brain networks can lead to a better understanding of network diseases such as TLE. Functional magnetic resonance imaging (fMRI) measures the blood oxygen level changes as a response to tasks performed, shown as activated areas in cortical brain regions (9). The neural signal network refers to the study of the interconnection and functional integration of neural signals when the brain is in a certain functional state, including effective connectivity (10,11). Effective connectivity describes whether activity in one region has a causal influence on activity in another region. It provides the ability to test causal models regarding the interactions between regions (9). This study aims to analyse brain activation and effective connectivity in TLE patients and healthy subjects during self-paced finger tapping using functional fMRI. Different cortical brain regions will be significantly activated during the finger tapping task.

MATERIALS AND METHODS

Procedures approved by the Human Research Ethics Committee of Universiti Sains Malaysia (approval number: USM/JEPeM/20060340, date: 03.01.2021) which complies with the Declaration of Helsinki. Consent for MRI and publications were obtained from subjects.

Subjects and Patients

A cross-study conducted at the radiology department of Hospital Universiti Sains Malaysia from 5th October 2016 until 4th October 2017 involved 12 healthy subjects and 12 TLE patients. Patients with TLE were above 18 years old, were clinically diagnosed with TLE, and were seizure free for at least 24 hours. Patients with brain lesions, history of alcohol and drug abuse, severe cognitive impairment or mental disorder, and post temporal lobe resection surgery were excluded from this study. Healthy subjects were 18 years old and above with no systemic disease or neurological symptoms. Patients with post brain trauma or surgery were excluded.

fMRI Acquisition

Each healthy subject and patient lay supine in the gantry of the MRI machine (Phillips 3 Tesla Achieva MR scanner, Best, The Netherlands). T1-weighted imaging sequence for brain structure was performed. The stimulus (picture of the right hand, left hand, or bilateral hands) was back-projected onto a computer screen that could be viewed through a mirror attached to the scanner's head coil above. Blood oxygen level-dependent (BOLD) fMRI, using a T2-weighted gradient echo planar imaging sequence, was acquired when the patients started self-paced finger tapping (right/left/bilateral) according to the stimulus projected in front of them. The protocol for finger tapping followed the paradigm protocol [total duration: 13 minutes, time to repeat (TR): 2 seconds, number of slices: 35, slice thickness: 3, voxel size: 2x2x3].

Image Analysis

Data were collected in Digital Imaging and Communications in Medicine format. Data were converted to NIfTI format using MRIConvert version 2.1.0 build 440, 2013, University of Oregon, Lewis Center for Neuroimaging. Statistical Parametric Mapping (SPM12) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London) software packages on the platform MATLAB 7.4-R2018b (Mathworks Inc., Natick, MA, USA) were used for pre-processing, i.e., smoothing, realigning, and normalizing the images so that all the images are standardized. First-level analysis was performed to observe the area of activation in each group. Activated regions were localized using Montreal Neurological Institute coordinates and assigned with the Neuromorphometrics Atlas in SPM. Second level analysis was performed to compare the difference in brain activation between TLE patients and healthy subjects across individuals.

For effective connectivity, the dynamic causal modelling (DCM) function was used in the SPM12 software. Bayesian Model Selection (BMS) in DCM was used to analyze the interaction between the visual and motor areas of the right and left brain in both groups. Three models were tested: bidirectional; from visual to motor; and from motor to visual.

Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

Statistical Analysis

Descriptive statistic to analyse demographic data. Maps of activation are compared between groups by means of two-sample t-tests as implemented in the SPM12 software. All maps are reported at a level of $p<0.001$ uncorrected, with only clusters passing a threshold of $p<0.05$ familywise error rate (FEW) corrected are shown.

Effective connectivity was analysed using the novel method of BMS, fixed function analysis (FFX) for group studies as implemented in DCM.

RESULTS

Demographic Findings

The mean age for healthy subjects was 36 years, while for TLE patients, it was 35 years. The youngest healthy subjects were 21 years and the oldest were 51 years with a standard deviation of 9.8. The youngest TLE patient was 25, and the oldest was 52 years, with a standard deviation of 8.3. The majority of the participants were female, 75% for healthy subjects and 92% for TLE patients. Demographic findings are summarised in Table 1.

Table 1. Demographic data of participant according to healthy and TLE

Variable	Study group	
	Healthy	**TLE**
Age, year		
Mean	36.2	35.3
Standard deviation	9.8	8.3
Minimum	21	25
Maximum	51	52
Gender, n (%)		
Female	9 (75)	10 (91.7)
Male	3 (25)	1 (8.3)

TLE: Temporal lobe epilepsy

Brain Activation

The areas within the brain cortex that were significantly activated were at the occipital region, as shown in Figure 1. This was the same for healthy individuals, and TLE patients. For first level analysis, more areas within the brain cortex were significantly activated in healthy subjects as compared to TLE subjects (all maps were reported at a level of $p<0.001$ uncorrected with only clusters passing a threshold of $p<0.05$ FWE corrected were shown). Table 2 and Table 3 show all the areas that have significant activation in healthy subjects and TLE patients, respectively. Regarding specific areas of activation, in healthy subjects, the right and left cuneus were the most active brain areas in the brain with peak values (T-values) of 13.27 and
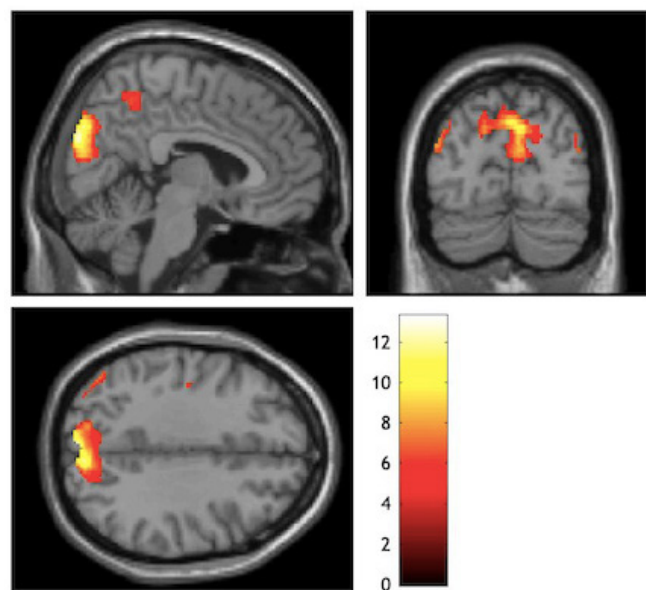
Figure 1. Rendered image for healthy subjects during bilateral finger tapping. This image shows intense activation at the bilateral occipital lobe, where the primary visual cortices are located [the higher the value, the higher the peak value (T-value) for activation as represented by colour coding].

Table 2. Activation in healthy subjects during bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)
	x	y	z	
Left cuneus	-6	-88	32	13.27
Right cuneus	6	-84	26	12.36
Left middle occipital lobe	-47	-74	26	8.05
Left precuneus	-1	-49	53	7.92
Right angular gyrus	47	-69	38	7.00
Left lateral ventricle	-27	-57	8	6.66
Right precuneus	18	-59	14	6.63
Right middle occipital lobe	45	-78	20	6.52
Right lingual gyrus	16	-42	-7	5.86
Left cerebral white matter	-35	-43	-13	5.77
Right post central gyrus	45	-11	32	5.76
Left post central gyrus	-42	-13	35	5.21

Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

Table 3. Activation in TLE patients during bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)
	x	y	z	
Right cuneus	6	-81	26	6.53
Left precuneus	-11	-69	26	6.05
Right middle occipital lobe	49	-71	29	5.45
Right superior frontal medial segment	1	56	14	5.16
Right cerebral white matter	16	-79	26	5.07
Right angular gyrus	57	-61	26	4.98
Right precuneus	9	-52	11	4.94

TLE: Temporal lobe epilepsy

Table 4. Areas that are significantly more activated in healthy subjects compared to the TLE patients in unilateral and bilateral finger tapping

Anatomical landmark	Coordinate			Peak level (T)	p
	x	y	z		
Left inferior occipital lobe	-42	-69	8	131.92	0.001
Right lingual gyrus	20	-40	-7	108.21	0.002
Left postcentral medial segment	-9	-38	-9	65.74	0.018
Right cerebral white matter	21	-73	-4	63.05	0.021
Left lingual gyrus	-3	-79	-1	62.46	0.022

TLE: Temporal lobe epilepsy

12.36, respectively. In TLE subjects, the most active areas during finger tapping were the right cuneus and the left pre-cuneus, with peak values (T-values) of 6.53 and 6.05, respectively. In healthy subjects, there was significant activation in bilateral motor areas (the right and left post central gyrus) with peak value of 5.76 and 5.21. However, no significant activation of the motor areas can be observed in TLE subjects. Second level analysis compared both groups using the means of two-sample t-tests as implemented in the SPM12 software. In the condition where the healthy state is more activated than TLE (Healthy > TLE), a few areas were shown to be significantly activated, as displayed in Table 4. The areas were left inferior occipital, right lingual gyrus, left medial segment of the postcentral gyrus, right cerebral white matter, and left lingual gyrus. For condition TLE is more activated than healthy (TLE > Healthy), no suprathreshold clusters was found.

Effective Connectivity

The influence between visual and motor nodes was tested using effective connectivity. For the visual node, cuneus (coordinate; right brain hemisphere x 6 y -84 z 26, left brain hemisphere x -7 y -86 z 31) was set as the coordinate of interest. Meanwhile, for the motor node, post central gyrus (coordinate; right brain hemispherex 45 y -11 z 32, left brain hemisphere x -42 y -14 z 35). The representative diagram shown in Figure 2. Three models were tested using DCM for BMS: fixed effect analysis. The models were bidirectional, visual to motor, and motor to visual, indicating whether motor and visual are influencing each other. In the bilateral hemispheres of healthy subjects, visual input has more influence on motor function, with the second model being the dominant one, as shown in Figure 3. The average value, 0.03 Hz, was equal bilaterally, 0.03 Hz. In right brain hemisphere of TLE subjects, the motor area exerts more influence on
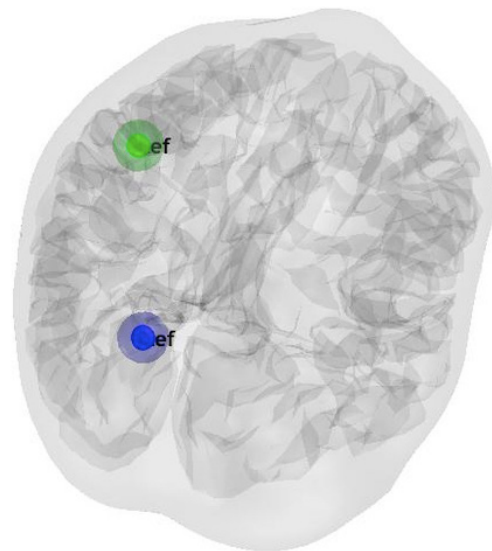
Figure 2. Nodes selected for effective connectivity (ef), left brain cuneus (blue circle) and post central gyrus (green). The same nodes were selected for the right brain hemisphere.

the visual area, as the third model was dominant as shown in Figure 4. The average value was 0.06 Hz. On the left-brain hemisphere, the dominant model was the same as in healthy subjects; the visual influences the motor processes more significantly. However, the average value was higher: 0.1 Hz. The effective connectivity between postcentral gyrus and cuneus in TLE patients is represented in Figure 5.

Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

Bayesian Model Selection: FFX
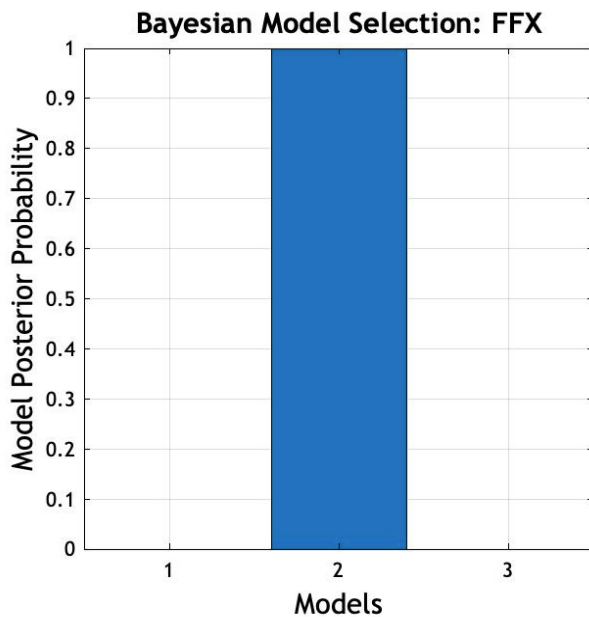
Figure 3. Bayesian model selection: fixed function analysis (FFX) bar chart for dominant model in bilateral brain's hemisphere for healthy subjects and left brain's hemisphere for TLE patients. Model 1: Bidirectional, Model 2: from cuneus to postcentral gyrus, Model 3: From Postcentral gyrus to cuneus.

TLE: Temporal lobe epilepsy

Bayesian Model Selection: FFX
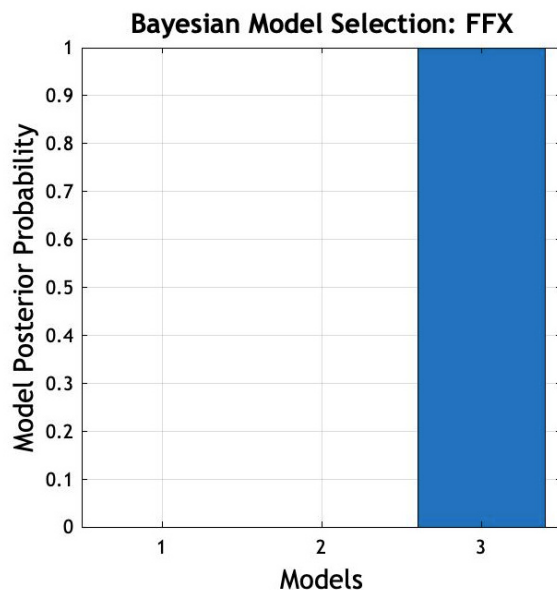
Figure 4. Bayesian model selection: fixed function analysis (FFX) bar chart for winning model in right brain's hemisphere for TLE patients. Model 1: Bidirectional, Model 2: From cuneus to Postcentral gyrus, Model 3: From Postcentral gyrus to cuneus.

TLE: Temporal lobe epilepsy
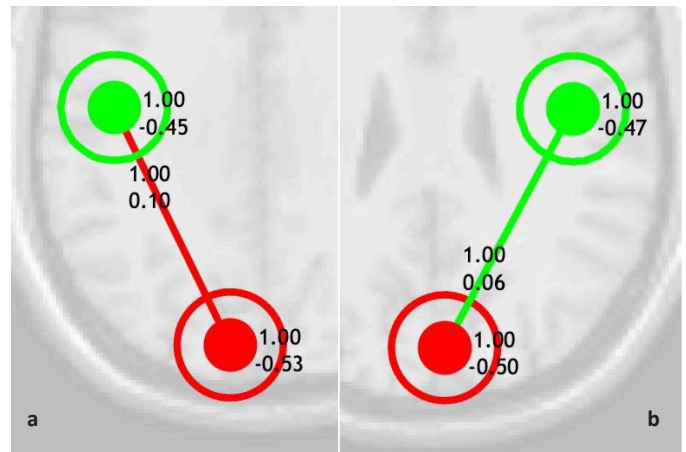
Figure 5 (a,b). Right and Left cerebral effective connectivity in TLE patients (green circle: postcentral gyrus, red circle: cuneus, numbers within the green and red circle represent effective connectivity within the region itself while the numbers at the green and red line represent the effective connectivity in between regions).

TLE: Temporal lobe epilepsy

DISCUSSION

The electrical activity of neurons and neuron clusters is the basis of cortical excitability, which is closely related to the tasks performed (12). The blood oxygen level is also changing in response to those tasks. In this study, the most activated region in the brain during visual cued self-paced finger tapping was in the occipital region, which is the visual area (13). This phenomenon was observed in both healthy and TLE subjects. The cue for finger tapping was a back-projected picture to the patients in the MRI. When the subjects saw the picture, they started the finger tapping task. We postulated that the intense activation in the visual region was due to the significant focus on the visual activity in order to perform the task fluently. Theoretically, during a motor task such as finger tapping in normal subjects, previous studies have shown that Primary Sensorimotor Cortex (SM1), Supplementary Motor Area (SMA), Basal Ganglia (BG), and Cerebellum were activated (14-16). From the first level analysis, there was not much activation seen in the motor areas as described in previous studies except for the group of healthy subjects, where significant activation was seen in bilateral primary motor areas. However, there were no significantly activated areas in the expected motor region observed in the subjects with TLE. This is the observation when the significance level was set to 0.05 FWE. Only if the significance level was set to 0.001 (uncorrected) did the motor areas become activated. The most common measure of Type I error over multiple tests is the "familywise error rate", abbreviated FWE. FWE is the chance of one or more false positives anywhere in the image. With a valid FWE =0.05 threshold, there is 95% confidence that there are no false positive voxels (or clusters) in the threshold map (9). Since there are activations in the motor areas when p=0.001, but not at p=0.05, the changes might not be strong enough to be significant.

In general, there are more areas with significant activation observed in healthy subjects than in TLE patients. The value for peak activation was also noted to be higher in healthy subjects. The second level

Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

analysis was performed to compare means between the groups to prove the observation that there are more areas of activation in healthy subjects than in TLE subjects during the finger-tapping task, or vice versa. In the condition where healthy subjects are more activated than TLE (healthy > TLE), a few areas in healthy subjects were activated more significantly than in TLE patients. The areas are left inferior occipital gyrus, right lingual gyrus, left medial segment postcentral gyrus, right cerebral white matter, and left lingual gyrus, as shown in Table 4. In the condition where TLE is more activated than healthy (TLE > Healthy): TLE patients do not show any suprathreshold clusters. Reduced activation observed in TLE patients may be due to detrimental effects of seizure propagation from the seizure focus, causing patients to rely less on the epileptic hemisphere. Seizure propagation paths formed strong neuronal networks due to synchronous and repetitive activity during the ictal process, causing disruption in normal motor networks in the brain (17). In addition, although patients were taking a variety of anticonvulsant medications, previous studies have shown that these drugs can also decrease BOLD activity during task-based fMRI studies (18,19).

TLE is a network disease. The network can be characterized by inter-regional functional connectivity, i.e., BOLD signal correlations between any two regions (3). The interconnection and functional integration of neural signals in a particular functional state can be studied by neural network analysis, including effective connectivity (10,11). Effective connectivity describes whether activity in one region has a causal influence on activity in another region (9). In this study, self-paced finger tapping was cued by visual images. The flow of signals is thought to be from visual to motor as information is processed and relayed in the brain. Thus, the interest was to study the interconnection between the visual and motor areas. Yun et al. (20) found that there is a bidirectional influence between visual and motor functions in their controlled subjects. In this study, the cuneus was chosen as the visual node and the Postcentral Gyrus as the nearest motor node. Three models were analysed using BMS, with fixed function analysis applied in DCM. The models are bidirectional: visual to motor and motor to visual. In both brain hemispheres of healthy subjects, the dominant model involved visual to motor pathways, as shown in Figure 3. This suggests that in healthy subjects, the visual regions exert more influence on the motor area. The value is similar in both sides of the brain hemispheres. Interestingly, the contrary was seen within the right brain hemisphere of TLE subjects whereby the motor to visual was the dominant model, which means that the motor node exerts more influence on the visual node. In the left hemisphere, the dominant model was the same as in healthy subjects. The visual node exerts more influence on the motor node with a higher influence value. The majority of the TLE patients are right-handed, and the dominant area is the left hemisphere. Dominant hemisphere connections are generally stronger because of increased use. Therefore, they may be less susceptible to detrimental seizure activity. If non-dominant hemisphere connections were impacted by seizure activity, this might cause patients to rely more on the dominant hemisphere during motor task performance (17).

Hermann et al. (21) suggest that epilepsy affects the brain both during seizures and interictally due to progressive structural and functional changes in the brain related to syndrome-specific network variations. Previous studies using rat models of epilepsy have suggested that disinhibition may underlie seizure-induced changes in cortical motor map representations (22). Both decreases in GABAergic transmission and increases in glutamatergic transmission, which occur in humans with epilepsy, have been shown to influence the recruitment of additional motor regions through pre-existing cortico-cortical connections (23).

Study Limitations

This study includes small numbers of participants and is very specific to finger tapping as main stimulant to assess the areas of activation and connectivity. A further study which may involves larger sample size and multiple stimulants would be helpful to further characterise areas of activation activation and connectivity in the brain.

CONCLUSION

This study found that there was less area of brain that has significant activation in TLE patients during motor activity. TLE brains also exhibit different effective connectivity, in which, in the right hemisphere, the motor area exerts more influence on the visual area, and in the left hemisphere, the visual area exerts more influence on the motor area. These findings suggest that there is an alteration of the motor networks in TLE patients. Since there are changes in cortical activation which may contribute to motor deficits observed in TLE patients, this study suggests that longer periods of seizure freedom may reduce motor deficits.

Ethics

Ethics Committee Approval: Procedures approved by the Human Research Ethics Committee of Universiti Sains Malaysia (approval number: USM/JEPeM/20060340, date: 03.01.2021) which complies with the Declaration of Helsinki.

Informed Consent: Consent for MRI and publications were obtained from subjects.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.M.Y., M.E.A., H.M.A.R., Concept: B.M.Y., M.E.A., A.I.A.H., H.M.A.R., Design: B.M.Y., A.I.A.H., H.M.A.R., M.R.A.R., Data Collection or Processing: H.M.A.R., M.R.A.R., Analysis or Interpretation: M.R.A.R., A.I.A.H., M.R.A.R., Literature Search: B.M.Y., Writing: B.M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This project was funded by FRGS grant (FRGS/1/2015/SKK02/UNISZA/02/1).

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Gazi Med J 2025;36(2):124-130

Yusoff et al. Brain Connectivity in Finger Tapping For Epilepsy Patients

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Real Versus Virtual Classes: A Perspective from Medical Undergraduate Student's Point of View with Their Effectiveness in Learning

Gerçek ve Sanal Sınıflar: Tıp Lisans Öğrencisinin Öğrenmedeki Etkinliği ile Bakış Açısından Bir Bakış

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ABSTRACT

Objective: In March 2020, a nationwide lockdown due to the spread of Coronavirus Disease of 2019 infection in India was declared. To continue the learning process, the Medical Universities of India adopted online learning. This article aims to compare online live classes and traditional face-to-face classes based on the opinions of Bachelor of Medicine, Bachelor of Surgery (MBBS) undergraduates of South India and determine the acceptability of each of the methods.

Methods: Online survey of 364 MBBS undergraduates (UGs) of medical colleges of South India was conducted using a questionnaire. A validated questionnaire produced on Google Form, which contains 16 questions, was mailed to all the participants. Their replies were noted, and statistical evaluation was done on drawbacks, benefits, and preferences, based on their valuable opinions.

Results: A total of 364 UG students participated in the online survey willingly. 87.16% of the students used Microsoft Teams for online classes. 35.71% of participants had a good experience with online classes. The main advantage of the online classes was comfort (28.41%). The main disadvantage of online classes was Internet issues (26.49%). Out of 364 UG students, 71.43% felt physical classes were better than online classes. The main advantage of physical classes was attentiveness (23.42%). The main disadvantage was compromised social distancing, with 19.84%. A total of 37% UGs preferred online classes, while 63% preferred physical classes.

ÖZ

Amaç: Mart 2020'de Hindistan'da COVID-19 enfeksiyonunun yayılması nedeniyle ülke çapında bir kilitlenme ilan edildi. Öğrenme sürecine devam etmek için Hindistan Tıp Üniversiteleri çevrimiçi öğrenmeyi benimsedi. Bu makale, Güney Hindistan Tıp Fakültesi, Cerrahi Lisansı (MBBS) lisans öğrencilerinin görüşlerine dayalı olarak çevrimiçi canlı sınıfları ve geleneksel yüz yüze dersleri karşılaştırmayı ve yöntemlerin her birinin kabul edilebilirliğini belirlemeyi amaçlamaktadır.

Yöntemler: Güney Hindistan Tıp Fakülteleri'nde okuyan 364 MBBS lisans öğrencisi (LÖ) ile çevrimiçi anket bir anket kullanılarak gerçekleştirildi. Google Form üzerinden oluşturulan ve 16 sorudan oluşan doğrulanmış bir anket tüm katılımcılara postalandı. Cevapları not edildi ve değerli görüşlerine dayanarak dezavantajlar, faydalar ve tercihler üzerinde istatistiksel değerlendirme yapıldı.

Bulgular: Toplam 364 LÖ öğrencisi çevrimiçi ankete gönüllü olarak katılmıştır. Öğrencilerin %87,16'sı çevrimiçi dersler için Microsoft Teams kullandı. Katılımcıların %35,71'i çevrimiçi derslerle ilgili iyi bir deneyim yaşamıştır. Çevrimiçi derslerin en büyük avantajı konfor (%28,41) oldu. Çevrimiçi derslerin en büyük dezavantajı İnternet sorunlarıydı (%26,49). Üç yüz altmış dört LÖ öğrencisinden % 71,43'ü fiziksel derslerin çevrimiçi derslerden daha iyi olduğunu düşünüyordu. Fiziksel sınıfların en büyük avantajı dikkat (%23,42) idi. En büyük dezavantaj ise %19,84 ile sosyal mesafenin bozulmasıydı. Toplamda %37'si LÖ'ler çevrimiçi dersleri tercih ederken, % 63'ü fiziksel dersleri tercih etti.

Gazi Med J 2025;36(2):131-135

Lochab et al. Real Versus Virtual Classes: Student's Perspective

ABSTRACT

Conclusion: Our study identifies both pros and cons for physical and online modes of teaching. However, UG students preferred physical classes more than online mode.

Keywords: Online classes, physical classes, universities, physical distancing, questionnaires

ÖZ

Sonuç: Çalışmamız, fiziksel ve çevrimiçi öğretim biçimlerinin hem artılarını hem de eksilerini tanımlamaktadır. Ancak, LÖ öğrencileri çevrimiçi moddan çok fiziksel dersleri tercih etti.

Anahtar Sözcükler: Çevrim içi dersler, yüz yüze dersler, üniversiteler, fiziksel mesafe, anketler

INTRODUCTION

Coronavirus Disease of 2019 was announced as a pandemic in March 2020 by the World Health Organization. In the same month, the Hon'ble Prime Minister of India declared a nationwide lockdown to limit the spread of the infection by preventing crowding and following social distancing. All the schools and universities were shut down until further notice.

To continue the learning process, the universities took up the method of online teaching (virtual classes). It was a considerable challenge for a practical-based course like MBBS and bachelor of dental surgery (BDS) to be taught online (virtually) in a developing country like India, with limited resources in terms of electricity and internet connectivity.

Platforms like MS Teams, Impartus, Zoom, Cisco Webex, G-Meet, etc., were used to conduct online lectures. This marked a new approach in teaching methods for Bachelor of Medicine, Bachelor of Surgery (MBBS) and BDS. However, this revolution had advantages and disadvantages from the perspective of undergraduates (UGs) as well as teachers.

Online learning is admired by all categories of students due to its asynchronous nature. Because of its asynchronicity, students can join the course when it is convenient for them. An additional benefit of online education is that it is cost effective (1). On the contrary, there may be a greater danger of compartmentalization and fragmentation than may be evidenced by classroom studies, and studies show that online teaching requires more work on the part of both students and teachers (2,3).

This transition opens ways for new teaching and learning processes, but at the same time, it requires adaptation to the new teaching process which might seem difficult for many people (4,5).

Online teaching also helps reduce the maintenance cost of institutions, decrease the time required for teaching, and decrease the cost of education; therefore, increasing enrollment (6). It may help the students never miss any classes due to health problems, weather problems, distance problems, or any other valid reason. It will help in the technological development of students and also keep them updated with global advancements (7). At the same time, the teachers, as well as UGs, were used to the traditional in-person one-to-one method of teaching, and it may be difficult for both to adapt.

The aim of this study was to find out the UG spoint of view regarding these methods of teaching. If the online (virtual) method is widely accepted, institutions can further integrate it into their routine teaching. This study will help the institutions decide what is better for students in terms of health and knowledge, and further help them choose either or both of the teaching methods.

MATERIALS AND METHODS

Study Type

Cross-sectional study.

Sample Size

Out of 2500 UGs, 364 MBBS and BDS UGs of 1st, 2nd, 3rd, and 4th year from 21 Medical Colleges of South India participated in the study.

Sample size was calculated using effect size 0.6, power 80%, alpha error 0.05, and a 5% significance level.

Using the formula: n=z2 X Ƃ2 /d2

Where,

n=Sample needed

z=Value of normal standard distribution

Ƃ=Standard deviation

d=Absolute precision

Inclusion Criteria

1. Students who have attended online classes.

Exclusion Criteria

1. Postgraduates or UGs who were not attending the online classes were eliminated from the study.

Tools Used

This study was conducted through an electronic questionnaire using Google Forms.

Detailed Description of the Procedure

Institutional Ethics Committee approval was obtained before conducting this study (approval number: IEC: 385/2020, date: 10.07.2020). Consent from all participants was obtained electronically, and they were informed that their data would remain confidential. The study was carried out from the 20 August 2020 (4 months after initiation of online classes) to the 7 December 2020. All the students were given the link to an online questionnaire using Google Forms. The questionnaire consisted of many questions mainly to assess the opinions of UGs on the disadvantages and advantages of online and physical classes, as well as their suggestions.

Statistics Analysis

The data obtained were analyzed using Microsoft Excel as percentages.

Gazi Med J 2025;36(2):131-135

Lochab et al. Real Versus Virtual Classes: Student's Perspective

RESULTS

A total of 364 UG students took part in the online survey willingly. Out of them, 60.71% were in 1st year, 23.08% in 2nd year, 13.19% in 3rd and 3.02% in 4th year of their respective courses.

The highest (87.16%) proportion of students used Microsoft Teams for online classes as shown in Figure 1.

Out of 364 UG students, 35.71% had a good experience with online classes, as shown in Figure 2. Advantages of online classes according to UGs were comfort (28.41%), followed by easy accessibility (17.90%), accessing all pages of slides (14.27%), looking up meanings of difficult words during class (12.52%), and fewer distractions (7.38%). Some also replied that having the opportunity is better than nothing: they are able to attend class on time, go back to the recordings and understand everything at their own pace, have better interaction, rewatch missed parts, have no hesitation in asking doubts, and have more time to study. Disadvantages of Online classes according to UGs were internet issues (26.49%), eye strain (22.46%), less attentiveness (17.66%), and less interaction with students/teachers (16.31%). Some also replied that there was no will to study; ineffective learning; no reduction in fees; the pace of the classes makes it difficult to write notes; a lack of the learning environment that exists in a classroom; that online classes are not the best option for professional courses like MBBS.
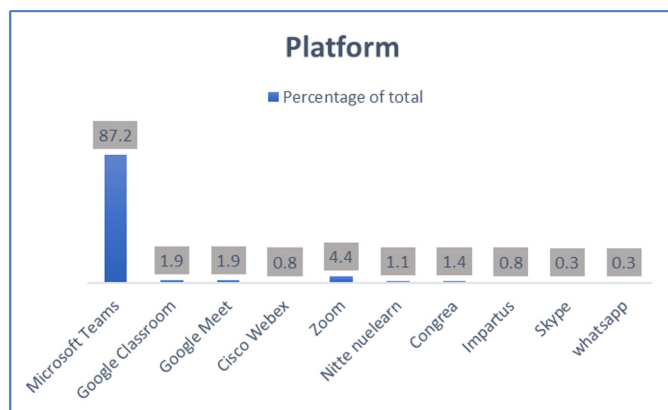
Figure 1. Showing proportion of students used which platform for their Online classes.
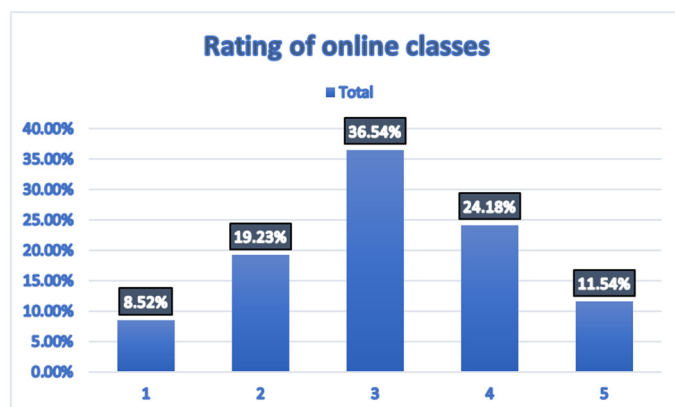
Figure 2. Showing rating of online classes by students.

Out of 364 UG students, 71.43% felt physical classes were better than online classes, as shown in Table 1. Advantages of physical classes according to UGs were attentiveness (23.42%), active learning (22.51%), more interaction (18.76%), and competitive spirit (15.74%). Some also replied that they were geared up for studying and discussions with friends. Disadvantages of physical classes according to UGs were compromised social distancing (19.84%), missing points during lecture (17.42%), difficulty due to extreme weather conditions (13.73%), delay due to travel (10.84%), and more distraction (8.88%). Some also replied that the recorded lecture was not available for revision.

For theory, 37% of undergraduate students preferred online classes, and 63% preferred physical classes.

62.09% of students felt that they were not attentive in online classes compared to physical classes, as shown in Table 2. 51.37% of UGs felt that their doubts were solved in online classes, 20.88% were unsure, and 27.75% felt otherwise. 48.90% of UGs agreed to attend classes from their hostel rooms, 20.88% were unsure, and 30.22% didn't agree.

52.47% of UGs accepted taking practicals simultaneously with theory classes, while 36.54% agreed to practicals being taken in a group at the end of a fixed period (e.g., blocks or semesters), and 9.07% agreed to attend practicals online.

Out of the total, 77.47% of UGs agreed that their teachers encourage them to use other forms of information like videos, books, research papers, etc., as shown in Figure 3.

DISCUSSION

During the global pandemic, many colleges and universities have started online classes. Now, many institutions are using this as a hybrid mode of teaching. There are pros and cons of both physical and online teaching.

Cipriano et al. (8) introduced an online curriculum for their students in a university-based dermatology clerkship. He found that students' opinions were overwhelmingly positive regarding the curriculum's

Table 1. Showing percentage and no. of students rating of physical classes over online classes

Rating of physical classes over online classes	Number of undergraduates	Percentage
Worst	22	6.04
Worse	36	9.89
Moderate	46	12.64
Better	82	22.53
Best	178	48.90

Table 2. Showing percentage and no. of students attentive in online classes as compared to physical classes

Whether students feel more attentive in online classes than physical classes	Number of undergraduates	Percentage
Yes	88	24.18
No	226	62.09
Maybe	50	13.74

Gazi Med J 2025;36(2):131-135

Lochab et al. Real Versus Virtual Classes: Student's Perspective
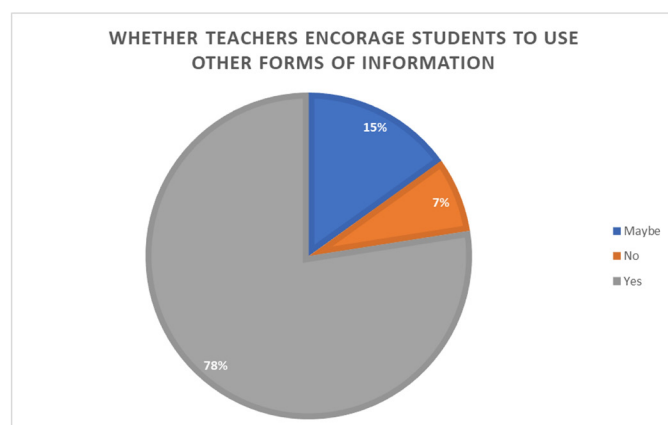
Figure 3. Showing whether teachers encourage students to use other forms of information like videos, books, research papers, etc.

usability and satisfaction. In our study, 71.43% of students felt that physical classes were better than online classes. This might be because Cipriano et al. (8) conducted the study in California, and we conducted our study in South India. The age of students could explain why, in India, students need more support, so they felt physical classes are much better than online classes.

Diaz and Cartnal (9) found that online learning courses often lead to social isolation and require better student reliance on independent learning skills. Students who need less support for learning are better suited to the online learning set-up. Jaggars (10) found that students stated that, in online courses, instructors are not always present and they need to teach themselves a lot. Hence, many students prefer taking easy subjects online and tackling complicated or principal subjects face-to-face (10). In our study, 16.31% of students reported less interaction with students/teachers. Some also replied that they had no will to study and experienced ineffective learning in online classes. Our study also shows that, most students do not like to attend online classes as it has more disadvantages than advantages.

Almahasees et al. (11) conducted a study in Jordan. They taught the students online for 4 months. They conducted two online surveys to explore students' experiences with the learning process that happened during those 4 months without any physical interactions. They randomly selected 280 students to investigate the efficiency, challenges, and benefits of online teaching. The analysis revealed that Zoom and Microsoft Teams were the common online platforms for online classes. In their study, students agreed that online education is beneficial during the pandemic. At the same time, students have mentioned that it is less effective compared to physical classes. Students mentioned that disadvantages of online learning are lack of interaction and motivation, technical issues, and Internet connectivity problems. They also mentioned some benefits of online teaching, such as self-learning, minimal expenses, convenience, and flexibility. They mentioned that online teaching could not substitute for physical learning. The authors recommend that amalgamated learning would be beneficial for providing a thorough learning ecosystem (11). In our study, tools used for online learning were Zoom, Microsoft Teams, Google Classroom, Google Meet, Cisco Webex, Impartus, etc. Disadvantages of online classes according to

our students were internet issues (26.49%), eye strain (22.46%), less attentiveness (17.66%), and less interaction with students/teachers (16.31%). Advantages of online classes, according to them, were comfort (28.41%), followed by easy accessibility (17.90%), accessing all pages of slides (14.27%). In our study, 71.43% of the students supported physical classes as compared to online classclasses.

Bast (12) conducted a survey on 1318 students to assess their insight into online teaching in contrast with traditional classroom teaching. They found that the benefits of online teaching, as mentioned by students, include flexibility, while the disadvantages include more distractions (12). Kulal and Nayak (13) conducted research on 203 students. Two separate structured questionnaires were given to students. Their study reveals that students are comfortable with online classes, but they do not consider that online classes will replace traditional classroom teaching. Technological issues were also noted as the key difficulty affecting the efficiency of the online classes. In our study, similar results were noticed. Students were not in favor of online classes due to numerous disadvantages.

Bali and Liu (14) conducted a study on 107 students about their views toward online teaching and face-to-face teaching from the perspective of social presence, social interaction, and satisfaction. They found that physical teaching experience was superior to online teaching with respect to social presence, social interaction, and satisfaction. They also found that few students were extremely comfortable in online teaching since it gave them the opportunity to be innovative by utilizing computer technology. In our study, 71.43% of students also felt physical classes were better than online classes. Students also mentioned more interaction in physical classes. They prefer physical classes over online classes.

Muthuprasad et al. (15) conducted a study on 307 students to understand their perception and preference towards online learning. They found that many of the respondents (70%) were eager to choose online classes. Their students mentioned that flexibility and accessibility of online classes make it more advantageous, however, internet problems in rural regions make it a challenge for students to access online education. The authors mentioned that the hybrid mode of teaching is beneficial. In our study, students also mentioned the flexibility of online classes as beneficial, but 26.49% of students mentioned internet issues as disadvantages of online classes, a finding similar to their results.

Mathera and Sarkans (16) conducted a survey on 313 students about online vs face-to-face learning. They found that flexibility, ease of access, the convenience of balancing personal, professional, and academic lives, and their desire to experience a new technique of education are the advantages of online learning. However, interaction with colleagues, teachers, and curriculum content was the key advantage of face-to-face learning. However, in their study, most participants (74%) mentioned that online education is their preferred modality. In our study, the advantages of both online and physical were the same as mentioned in their study, but 71.43% of the students preferred physical learning as compared to online learning.

Ridwan et al. (17) conducted a study on 35 students. They found that 80% of students mentioned internet network constraints due to uneven connections in each region. 94.3% of students mentioned that it is easier to learn in the classroom by interacting directly with

Gazi Med J 2025;36(2):131-135

Lochab et al. Real Versus Virtual Classes: Student's Perspective

teachers. In our study, 26.49% of students mentioned internet issues as disadvantages of online classes, and 18.76% mentioned that it is easier to learn in the classroom by interacting directly with teachers.

In addition, found that for theory classes 63% of students preferred physical classes; 9.07% agreed to attend practicals online both online and physical teaching have their pros and cons. Therefore, a blended or hybrid mode of learning is better for higher education institutions.

Strength and weakness the study has included 21 medical colleges from south India, so a wider population has been included. But in addition to students', faculty can also be included in the study to learn about their opinions on student learning during online and physical classes.

Study Limitations

Only South Indian colleges were included North Indian colleges were not included.

CONCLUSION

Üç yüz altmış dört undergraduate students participated in the online survey. A proportion of 87.16% of students used Microsoft Teams for online classes. 35.71% of students had a good experience with online classes. Advantages of Online classes according to UGs were Comfort, followed by easy accessibility and accessing all pages of slides disadvantages of online classes according to UGs were internet issues, eye strain, reduced attentiveness, and reduced interaction with students/teachers.

71.43% of students felt physical classes were better than online classes. UGs stated that the advantages of physical classes were attentiveness, active learning, and more interaction. Disadvantages of physical classes according to UGs were compromised social distancing, missing points during lecture, and distraction.

So, both online as well as physical teaching have their pros and cons so a blended or hybrid mode of learning is better for higher education in the institutions. Easy topics and revisions can be done online, while tough topics can be dealt with in physical classes. This will enhance student learning.

Ethics

Acknowledgement

Author Contributions

Surgical and Medical Practices: A.L., Concept: C.G., Design: C.G., Data Collection or Processing: A.L., Analysis or Interpretation: A.L., V.P., Literature Search: A.L., C.G., V.P., Writing: A.L., C.G., V.P.

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Alpha-Mangostin Provides Protection from Mucosal Damage via Prostaglandin E2 in Indomethacin and Ethanol-Induced Gastric Ulcers

Alfa-Mangostin, İndometasin ve Etanol Kaynaklı Gastrik Ülserlerde Prostaglandin E2 Aracılığıyla Mukozal Hasara Karşı Koruma Sağlar

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ABSTRACT

Objective: Gastric ulcer is frequently observed among the gastrointestinal diseases and is induced by various factors. Alpha-mangostin (α-MG) has antioxidant and anti-inflammatory properties and may prevent gastric ulcers. This study was conducted to evaluate the healing effect of α-MG against gastric ulcer caused by indomethacin (Ind) and ethanol (Eth) in rats.

Methods: Wistar albino male rats were used to establish the experimental model. Seven groups were formed, as group I sham, group II (5 mL/kg Eth), group III (100 mg/kg Ind), group IV (Eth + Lansoprazole (Lans) 30 mg/kg), group V (Ind + Lans 30 mg/kg), group VI (Eth + α-MG 10 mg/kg), and group VII (Ind + α-MG 10 mg/kg) (n=10). Cytokines; VEGF-A; NOS2/iNOS; PGE2 levels were analyzed by the ELISA method. Besides, the general appearance of the gastric tissues was evaluated by hematoxylin-eosin staining, COX-1, COX-2, NF-κB, and caspase-3 levels were measured immunohistochemical (IHC).

Results: Cytokine levels decreased in the treatment groups compared to the ulcer groups. There was a decrease in VEGF-A and NOS2/iNOS levels in the α-MG administered groups. The reduction in PGE2 levels in the gastric ulcer groups was counteracted by an increase in both the Lans and α-MG administered groups. In the IHC results, while COX-1, COX-2, NF-κB, and caspase-3 levels were increased in gastric ulcer groups, significant decreases were observed in Lans and α-MG groups.

ÖZ

Amaç: Gastrik ülser, gastrointestinal hastalıklar arasında sıklıkla görülür ve çeşitli faktörler tarafından tetiklenir. Alfa-mangostin (α-MG), antioksidan ve anti-inflamatuar özelliklere sahiptir ve gastrik ülseri önleyebilir. Bu çalışma, sıçanlarda indometazin (Ind) ve etanol (Eth) kaynaklı gastrik ülsere karşı α-MG'nin iyileştirici etkisini değerlendirildi.

Yöntemler: Deneysel modeli oluşturmak için Wistar albino erkek sıçanlar kullanıldı. Grup I sham, grup II (5 mL/kg Eth), grup III (100 mg/kg Ind), grup IV (Eth+Lansoprazol (Lans) 30 mg/kg), grup V (Ind + Lans 30 mg/kg), grup VI (Eth + α-MG 10 mg/kg) ve grup VII (Ind + α-MG 10 mg/kg) olmak üzere yedi grup oluşturuldu (n=10). Sitokinler, VEGF-A, NOS2/iNOS, PGE2 düzeyleri ELISA yöntemi ile analiz edildi. Ayrıca, gastrik dokuların genel görünümü hematoksilen-eozin boyama ile değerlendirildi, COX-1, COX-2, NF-κB ve kaspaz-3 düzeyleri immünohistokimyasal olarak ölçüldü.

Bulgular: Sitokin düzeyleri, ülser gruplarına kıyasla tedavi gruplarında azaldı. α-MG uygulanan gruplarda VEGF-A ve NOS2/iNOS düzeylerinde azalma oldu. Gastrik ülser gruplarında PGE2 düzeyindeki azalma, hem Lans hem de α-MG uygulanan gruplarda artış gösterdi. İmmünohistokimyasal sonuçlarda, COX-1, COX-2, NF-κB ve kaspaz-3 düzeyleri gastrik ülser gruplarında artarken, Lans ve α-MG gruplarında önemli düşüşler görüldü.

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Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries

ABSTRACT

Conclusion: As a result, α-MG eased inflammation and increased PGE2 levels. It reduced the levels of COX-1, COX-2, NF-κB, and caspase-3. As a result of these data, α-MG may be a potential therapeutic agent against gastric ulcer.

Keywords: Gastric ulcer, indomethacin, ethanol, alpha-mangostin, rat

ÖZ

Sonuç: Sonuç olarak, α-MG inflamasyonu hafifletti ve PGE2 düzeylerini artırdı. COX-1, COX-2, NF-κB ve kaspaz-3 seviyelerini düşürdü. Bu veriler sonucunda α-MG, mide ülserine karşı potansiyel bir tedavi edici ajan olabilir.

Anahtar Sözcükler: Mide ülseri, indometasin, etanol, alfa-mangostin, sıçan

INTRODUCTION

Peptic ulcers, the most common disease of the gastrointestinal tract, negatively affect many people worldwide (1). Ulceration is observed if there is an imbalance between mucosal defense factors [enzymatic and non-enzymatic antioxidants, mucus secretion, bicarbonate secretion, blood flow, and prostaglandins (PGs)] and aggressive gastric factors [acid-pepsin, leukotrienes, and reactive oxygen species (ROS)] (2,3). Non-steroidal anti-inflammatory drugs (NSAIDs, e.g., indomethacin (Ind)), alcohol consumption, *Helicobacter pylori (H. pylori)* infections, smoking, and emotional stress are among factors leading to ulcer formation (4). ROS, neutrophil infiltration, inflammation, and lesions in the gastric mucosa are involved in the pathogenesis of experimental ulcer induced by ethanol (Eth) and NSAIDs, [e.g., (Ind)] (5-7). Proton pump inhibitors (e.g., lansoprazole, lans), histamine type 2 receptor blockers (e.g., ranitidine), or mucosal protective agents (e.g., misoprostol) are recommended for ulcer treatment. However, these treatments also have potential side effects. Therefore, it is essential to identify new agents with lower side effects (8,9).

Medicinal plant extracts are sources for new biologically active molecules, and have shown promising results in the treatment of various pathologies, including gastric ulcers (6). Mangosteen (garcinia mangostana L.) is a widely used medicinal plant in Thailand, India, Sri Lanka, and Myanmar. Studies reveal antioxidant, antiallergic, antibacterial, anti-inflammatory, antitumoral, and antiviral activities (10,11). The biological properties of mangosteen are related to the xanthones isolated from different parts. Studies have revealed important xanthones such as alpha beta gamma-mangostin, garcinone E, 8-deoxgartanine, and gartanin in phytochemical analysis (12). Alpha-mangostin (α-MG) is the most common polyphenolic xanthan in garcinia mangostana (10). α-MG shows potential antitumor effects in various types of cancer (12-15). It also has anti-inflammatory (16), antioxidant, hypoallergenic, and antifungal activities (17, 18). It has also been proven to have many pharmacological activities, including cardioprotective, anti-diabetic, and neuroprotective properties (19,20).

α-MG has been investigated in some ulcer models, and some protective effects have been reported. Current evidence cannot explain the protective role of this xanthone on a gastric ulcer. We performed several biochemical and histopathological analyses by creating an ulcer model in animals with Eth and Ind to evaluate the anti-ulcer activity of α-MG.

MATERIALS AND METHODS

Drug

α-MG (MedChemExpress, NJ, USA), ETH (99% absolute), IND (Sigma-Aldrich, MO, USA), and Lans (Cayman Chemical, Michigan, USA) were purchased. All drugs were dissolved in dimethyl sulfoxide (DMSO) and administered intragastrically (i.g.) to the animals.

Animals and Ethical Approval

Seventy male Wistar albino rats (body weight 250-300 g) were obtained from Atatürk University Medical Experimental Practice and Research Center, and the ulcer model was carried out at this center. All animals were housed under standard humidity, temperature (22±2 °C), and 12-hour light/dark cycle conditions. Animals were fed standard pellet feed and fasted for 12 hours before starting the study, but they were allowed free access to water. All experiments were carried out following the permission of Atatürk University Animal Experiments Local Ethics Committee (approval number: 175, date: 17.09.2018).

Creating an Ulcer Model with Eth and Ind

Seventy Wistar albino male rats were used to evaluate the effects of α-MG on the gastric ulcer. Seven groups of 10 rats each were randomly formed. Experimental groups are as follows. After the gastric ulcer model was created, drugs (Lans and α-MG) were administered. After 90 minutes, the rats were sacrificed under anesthesia, and their stomachs were excised. Gastric tissues were incised along the small curvature and washed with saline to clear blood clots. Stomach tissues were kept in suitable storage conditions for biochemical and histopathological analysis.

Sham group; 750 μL/250 g b.w., DMSO, i.g. (21).

Eth group; 5 mL/kg, i.g. (22).

Ind group; 100 mg/kg, i.g. (21)

Eth + Lans group; respectively, 5 mL/kg+30 mg/kg, i.g. (23)

Ind + Lans group; respectively, 100 mg/kg+30 mg/kg, i.g. (24)

Eth + α-MG group; respectively, 5 mL/kg+10 mg/kg, i.g.

Ind + α-MG group; respectively, 100 mg/kg+10 mg/kg, i.g.

Biochemical Analysis

Gastric tissues were homogenized for 15 minutes, using phosphate buffer solution (PBS) in the cooled area. Homogenates were filtered and centrifuged at 4 °C. Supernatants were used for analysis. All experiments were carried out at room temperature. Tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-10, vascular endothelial growth factor A (VEGF-A), nitric oxide synthase 2 (NOS2)/inducible NOS (iNOS), and PG E2 (PGE2) levels were measured from gastric tissue by enzyme-linked immunosorbent test (ELISA). The parameters measured in the study were performed using rat TNF-α, IL-1β, IL-10, VEGF-A, NOS2/iNOS, and PGE2 ELISA test kits (Wuhan, China) according to the manufacturer's instructions.

Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries

Histopathological Method

Necropsy of the rats was performed, and the gastric tissues were fixed in 10% neutral formalin solution. Tissues were embedded in paraffin blocks after routine alcohol-xylol follow-up procedures. Sections of 5 μm, taken on poly-lysine slides, were stained with hematoxylin-eosin and evaluated as none (0), mild (1), moderate (2), and severe (3) for degenerative and ulcerative changes.

Immunohistochemical Method

Gastric tissues were fixed in 10% neutral formalin solution. Tissues were embedded in paraffin blocks after routine alcohol-xylol processing. After washing with PBS, 5 μm sections taken on poly-lysine slides were passed through xylene and alcohol-series. Then, endogenous peroxidase inactivation was achieved by keeping them in 3% H_2O_2 for 10 minutes. The antigen was treated with retrieval solution at 500 watts for two 5-minute intervals. Subsequently washed tissues with PBS Cyclooxygenase-1 (COX-1) (Santa Cruz, Catalog No, sc-19998 1/200 dilution ratio), COX-2 (Abcam, Catalog No ab15191, 1/200 dilution rate), nuclear factor kappa B (NF-κB) (Abcam, Catalog No ab7971, 1/200 dilution ratio), caspase 3 (Biorbyt, Catalog No Orb382909, 1/200 dilution ratio) with primary antibodies at room temperature for 20 minutes. Mouse and Rabbit Specific HRP/DAB immunohistochemical (IHC) Detection Kit-Micro-polymer Kit

(Abcam, Catalog No. ab236466) was used as the secondary antibody, as recommended by the manufacturer. DAB (3,3'-Diaminobenzidine) was used as the chromogen. After counterstaining with Mayer's Hematoxylin, it was covered with entellan and examined under a light microscope. Immune positivity in gastric tissues was examined as no (0 point), mild (1 point), moderate (2 point), and severe (3 point).

Statistical Analysis

SPSS v.20 (Chicago, USA) was used for all statistical analyses. The distribution of the data was evaluated using the Shapiro-Wilk test. One-way ANOVA was used for biochemical analysis. In histopathological findings, the Kruskal-Wallis test and Mann-Whitney U test were used to find differences between groups. A p-value less than 0.05 (<0.05) was considered statistically significant. Data were presented as mean ± SD. All graphs were drawn using GraphPad Prism v.8 (San Diego, USA).

RESULTS

Gastric Cytokine Levels

Cytokine levels of TNF-α, IL-1, and IL-10 in all groups are presented in Figure 1. In the experimental models created with Eth and Ind, TNF-α
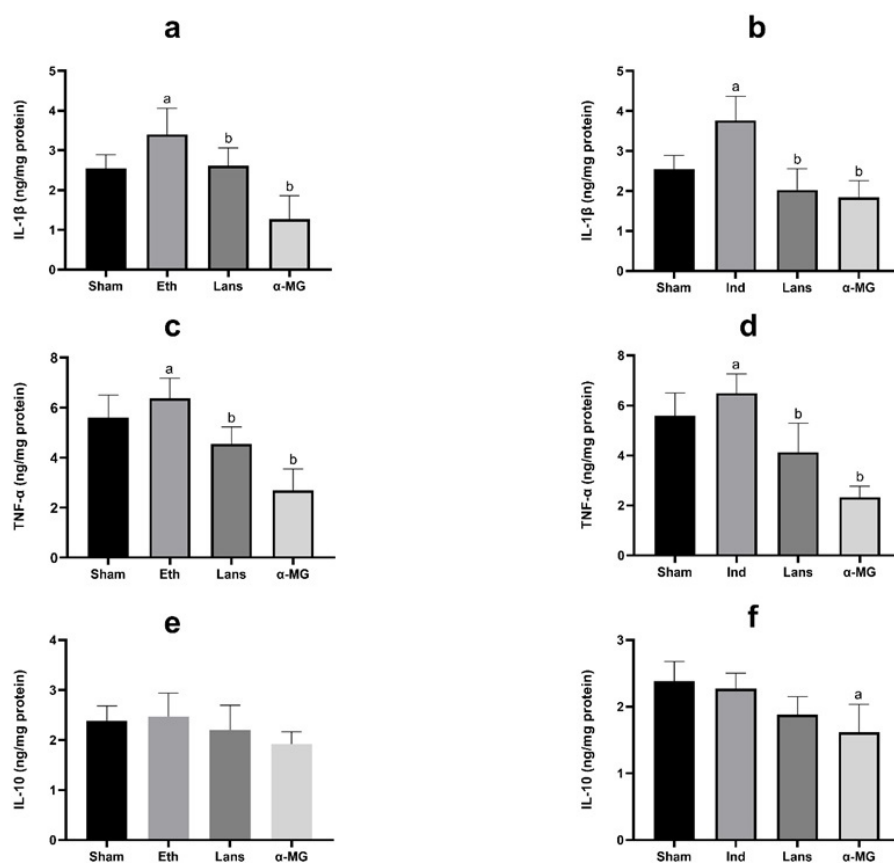
Figure 1. Cytokine levels were measured in the homogenized gastric tissues in the experimental groups. (a) IL-1β levels in the Eth group, (b) IL-1β levels in the Ind group, (c) TNF-α levels in the Eth group, (d) TNF-α levels in the Ind group, (e) IL-10 levels in the Eth group (f), IL-10 levels in the Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to the Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG; Alpha mangostin, TNF-α; Tumor necrosis factor-alpha, IL-1β, Interleukin-1 beta, IL-10: Interleukin 10

Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries

levels increased without significant difference compared to the sham group (p>0.05), while IL-1 levels increased significantly (p<0.05). The Lans and α-MG treatments decreased both proinflammatory cytokine levels (p<0.05). IL-10 levels did not change significantly in both ulcer models (p>0.05), but the decrease in IL-10 levels was significant in the Ind+α-MG group (p<0.05).

Gastric VEGF-A Levels

VEGF-A levels in all groups were determined in gastric tissues (Figure 2). There was no change in VEGF-A levels in ulcer groups created with Eth and Ind (p>0.05). However, in the Eth group, the α-MG treatment decreased VEGF-A levels (p<0.05). In the Ind group, the VEGF-A level decreased in both the model group and the group receiving α-MG treatment (p<0.05).

Gastric NOS2/iNOS Levels

NOS2/iNOS levels in all groups were determined in gastric tissue (Figure 3). No change was observed in NOS2/iNOS levels in the Eth group (p>0.05). However, we found significant reductions in the Lans-treated and α-MG-treated groups (p<0.05). NOS2/iNOS levels decreased in ulcer models with Ind (p<0.05), and a similar decrease was observed in Lans and α-MG groups (p<0.05).
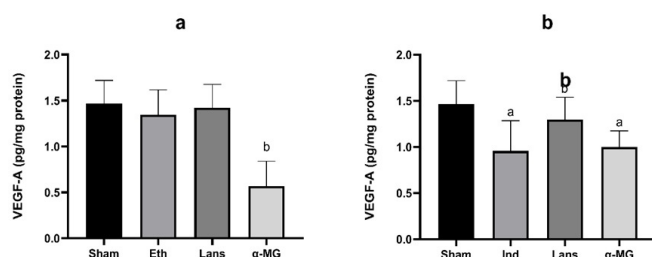
Figure 2. VEGF-A levels were measured in the gastric tissues homogenized from the experimental groups. (a) VEGF-A levels in Eth group (b) VEGF-A levels in Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, VEGF-A: vascular endothelial growth factor-A
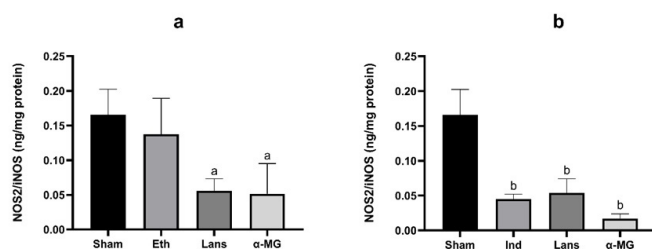
Figure 3. NOS2/iNOS levels were measured in the homogenized gastric tissues in the experimental groups. (a) NOS2/iNOS levels in the Eth model (b) NOS2/iNOS levels in the Ind model. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, NOS2/iNOS: Nitric oxide synthase 2/inducible NOS

Gastric PGE2 Levels

PGE2 levels in all groups were determined in gastric tissue (Figure 4). PGE2 levels decreased in both ulcer groups (p<0.05). The ulcer model created with Eth, Lans, and α-MG applications caused significant increases in PGE2 levels (p<0.05). In the Ind-induced ulcer model, while PGE2 level increased in the Lans-treated group (p<0.05), a slight increase was found in the α-MG-treated group (p>0.05).

Histopathological Staining

A statistically significant difference was found between the groups regarding degenerative and ulcerative changes in the gastric mucosa glands (Figure 5 and Figure 6). No degenerative or ulcerative findings were present in the epithelium and glands of the gastric mucosa of the animals in the sham group. While severe ulcerative changes were observed in the gastric mucosa in the Eth and Ind groups, it was found that ulcerative and degenerative changes decreased in the Eth + Lans, Ind + Lans, E + α-MG, and Ind + α-MG groups, and the gastric mucosa glands especially had a more regular structure (Figure 7).

Immunohistochemical Staining

There was a significant difference between the groups in terms of COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity in gastric tissues. COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity were not determined at a significant level in the gastric tissues of rats in the sham group. It was determined that COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity were severe in the gastric tissues of the animals in the Eth and Ind groups. Besides, the immunopositivity of COX-1, COX-2, NF-κB, and Caspase-3 were moderately in the Eth + Lans, Ind + Lans, Eth + α-MG, and Ind+αMG groups (Figure 7). Evaluation of immunopositivity is presented in Figure 5 and Figure 6.

DISCUSSION

Ulcer, a common disease of the gastrointestinal tract, is characterized by inflammatory lesions or mucosal injuries due to an imbalance between aggressive factors such as acid, *H. pylori*, pepsin, and defense factors, including bicarbonate ions, PGs, and gastric mucus (25). Gastric ulcers and gastritis are often seen in people who use NSAIDs, smoke, or drink alcohol (26). Gastric ulcers caused by Eth administration, occur due to its direct necrotizing effect on the
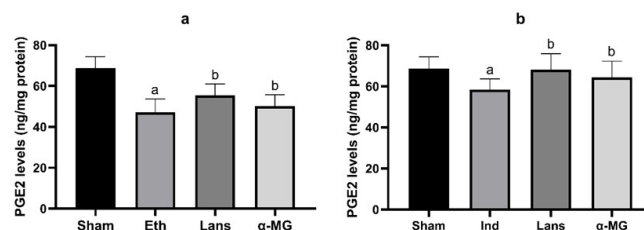
Figure 4. PGE2 levels were measured in the homogenized gastric tissues in the experimental groups. (a) PGE2 levels in the Eth group, (b) PGE2 levels in the Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin; PGE2: Prostaglandin

Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries
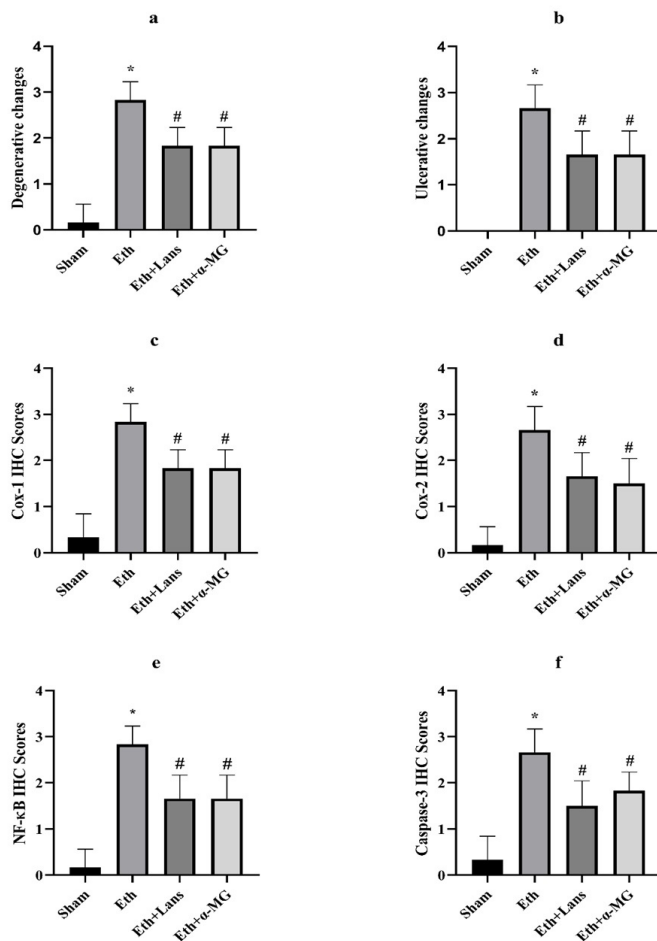
Figure 5. Scoring of immune staining in Eth-induced gastric ulcer model. (a) Degenerative changes and (b) ulcerative changes, (c) COX-1 and (d) COX-2, (e) NF-kB and (f) Caspase-3 IHC scores. Data are presented as mean±SD.

*p<0.05 compared to the sham group, #p<0.05 compared to the Eth group.

Eth: Ethanol, Lans: Lansaprazole; α-MG: Alpha mangostin, α-MG; COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kb: Nuclear factor kappa B

Figure 6. Scoring of immunostaining in the Ind-induced gastric ulcer model. (a) Degenerative changes and (b) ulcerative changes, (c) COX-1, (d) COX-2, (e) NF-kB, and (f) Caspase-3 IHC scores. Data are presented as mean ± SD.

*p<0.05 compared to the sham group, # p <0.05 compared to the Ind group.

Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kb: Nuclear factor kappa B

gastric mucosa. Moreover, Eth causes gastric lesions by disrupting the protective mucus/bicarbonate barrier and subsequent microcirculatory disorders, ischemia, and generation of free radicals, which damage the vascular endothelium (27). Regarding Ind, NSAIDs act by inhibiting COX-1 and COX-2 to promote a decrease in PG levels. Therefore, inhibition of PG synthesis results in the weakening of the mucosal defense (28).

Eth and Ind cause ulcerative lesions including deterioration in the structure of mucosal cells, hemorrhage, and edema by reducing the defensive factors that protect the gastric mucosa. α-MG reduces the ulcerative and degenerative effects that occur in the stomach in both gastric ulcer models. To explain α-MG's mechanism of actionα-MG, we focused on the PGE2 pathway inhibited by Eth and Ind. PGs, especially PGE2, protect the gastric mucosa through

the activation of different EP receptors, increasing mucus and bicarbonate secretion, increasing blood flow, and reducing acid secretion. Moreover, PGE2 deficiency causes neutrophil infiltration and activation of inflammatory pathways (29,30). Gastric PGE2 level decreases in Eth and Ind-induced gastric ulcers (31,32). The NF-κB signaling pathway contributes to gene expression control of multiple factors and plays an important role in cell stress response, apoptosis, immune response, inflammation, and cancer development (33). NF-κB contributes to the expression of inflammatory genes. Activation of neutrophils leads to increased expression of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (34). It has been shown that inhibition of NF-κB can contribute to ulcer healing in both ulcer models created with Eth and Ind (35,36). Besides cytokine regulation, NF-κB is also associated with iNOS expression and NO release (37). NO is

Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries
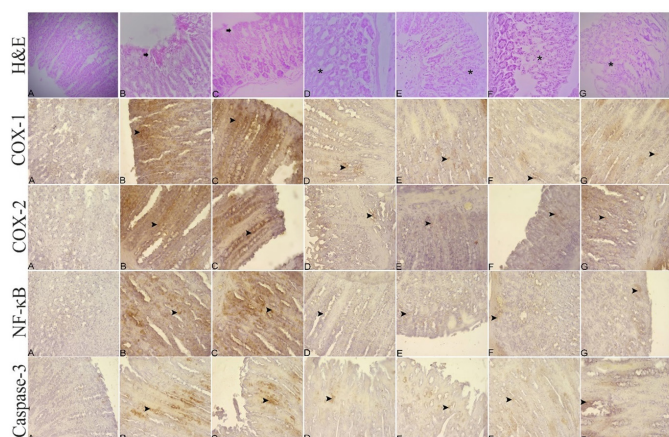
Figure 7. Evaluation of H&E staining and COX-1, COX-2, NF-kB and Caspase-3 immune positivity in gastric ulcer induced by Eth and Ind. (A) Sham group, (B) Eth group, (C) Ind group, (D) Eth + Lans group, (E) Ind + Lans group, (F) Eth + α-MG group, (G) Ind + α-MG group. Gastric mucous glands and immunopositivity respectively was indicated by star and arrowhead.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kB: Nuclear factor kappa B

part of the gastrointestinal mucosal defense but also contributes to mucosal damage (38). Overexpression of NO can cause cell damage by interacting with other radicals and injure the gastric mucosa. High NOS2 levels may lead to secretion of large amounts of NO and severe damage to many tissue types (39,40). In previous studies, α-MG significantly inhibited the production of NO, TNF-α, PGE2, and iNOS in some cell lines stimulated with lipopolysaccharide (17). In our study, NOS2 levels in the gastric mucosa decreased in both model groups, and a similar decrease was observed in the α-MG treated groups. The healing effect of α-MG was also accompanied by anti-inflammatory activity. α-MG decreased TNF-α, IL-1β, and NOS2/iNOS levels in gastric tissues of ulcerated animals. This is in line with previous studies showing that α-MG can modulate the inflammatory cytokine and mediator production under inflammatory conditions (41-43).

Gastric mucosa damage also brings vascular damage to ulcerated areas. At this point, angiogenesis facilitates ulcer healing by playing an important role in accelerating ulcer healing because nutrient delivery to the healing tissue is maintained (44). The main trigger of this change is tissue hypoxia, which stimulates genes encoding angiogenic growth factors such as VEGF. As a result, endothelial cells from micro vessels preserved at the injury site migrate, proliferate, and ultimately form a microvascular network (45). VEGF-A from the VEGF family plays a key role in blood vessel growth (46). VEGF-A levels were slightly decreased in both ulcer models we used in this study. A significant decrease in VEGF-A levels was also detected in the α-MG treatment groups. In another study, it has been shown that α-MG can increase the VEGF level depending on time, and this situation can occur in a time-dependent manner (47). In the same study, it was reported that α-MG can bind superoxide radicals, remove them from the environment, and increase the VEGF level by increasing NO levels (47).

Caspase-3 activation contributes to the disruption of mucosal integrity due to pathological events that occur during epithelial cell damage, cell cytotoxicity, or mitochondrial damage caused by both NSAIDs and Eth (48,49). Caspases, a family of cysteine proteases, play a critical role in the execution of apoptosis. Caspase-3 is not only a promoter but also a marker for apoptosis. It has been demonstrated that α-MG suppresses the IHC expression of caspase-3 in ulcer models. α-MG could reduce cell damage by inhibiting several enzymes involved in the apoptotic cascade. As a result, α-MG can reduce the gastric injuries induced by Ind and Eth. α-MG is a natural polyphenolic xanthone and affects NO release and inhibits COX-1 and COX-2. Based on the evidence obtained, α-MG can be expressed as a protective and healing agent for gastric ulcers through different mechanisms. However, a series of molecular analyses is needed for clearer results.

Ethics

Acknowledgement

Footnotes

Authorship Contributions

Concept: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Design: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Supervision: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Resources: E.E., A.T., M.C.G., Material: E.E., B.B., A.T., M.C.G., Data Collection or Processing: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Analysis or Interpretation: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Literature Search: E.E., B.B., A.T., M.C.G., Writing: E.E., B.B., M.C.G., Critical Review: E.E., B.B., A.T., M.C.G., Y.B., S.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Gazi Med J 2025;36(2):136-143

Eraslan et al. Alpha-Mangostin Can Alleviates Stomach İnjuries

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Gazi Med J 2025;36(2):136-143

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Evaluation of Healthy Lifestyle Behavior of Family Physicians and Lifestyle Medicine in Their Clinical Practice

Aile Hekimlerinin Sağlıklı Yaşam Biçimi Davranışlarının ve Klinik Uygulamalarında Yaşam Biçimi Tıbbının Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to assess the healthy lifestyle behavior of family physicians (FPs) and their engagement in lifestyle medicine practices within their clinical practice.

Methods: An online questionnaire was developed to collect responses from FPs between July 2018 and August 2019. A descriptive and correlational design was employed. The questionnaire consisted of two parts: "personal information of participants" and "the Healthy Lifestyle Behavior Scale-II". The survey was conducted using an e-survey platform, and targeted a convenience sample of FPs from eight countries in a cross-sectional study. Participants were provided with information about the survey length, data storage procedures, duration of storage, the identity of the investigators, and the purpose of the study.

Results: The study included 131 FPs, with a higher proportion of male participants. The frequency of smoking was found to be significantly higher among Turkish FPs (p=0.013). However, no statistically significant difference was observed among FPs in terms of the total score on the scale or the scores on the six dimensions.

Conclusion: The majority of FPs expressed a desire for further education, suggesting a need to incorporate educational interventions into medical school curricula. Additionally, well-structured web-based massive open online courses could serve a solution to meet the educational needs of FPs in the realm of healthy lifestyle behaviors and lifestyle medicine practices.

Keywords: Lifestyle medicine, family medicine, clinical practice

ÖZ

Amaç: Bu çalışmanın amacı, aile hekimlerinin sağlıklı yaşam biçimi davranışlarını değerlendirmek ve klinik uygulamalarında yaşam biçimi tıbbına yönelik katılımlarını incelemektir.

Yöntemler: Temmuz 2018 ile Ağustos 2019 tarihleri arasında aile hekimlerinden veri toplamak amacıyla çevrimiçi bir anket geliştirildi. Tanımlayıcı ve korelasyonel bir araştırma deseni kullanıldı. Çalışmada uygulanan anket, "katılımcıların kişisel bilgileri" ve "Sağlıklı Yaşam Biçimleri Davranış Ölçeği-II"i içermektedir. Kesitsel bir çalışma olarak tasarlanan bu araştırmada, örneklem kolayda örnekleme metodu ile sekiz ülkeden belirlenmiştir, ve anketler katılımcılara elektronik ortamda uygulanmıştır. Katılımcılara anketin süresi, veri saklama işlemleri, saklama süresi, araştırmacıların kimliği ve çalışmanın amacı hakkında bilgi verilmiştir.

Bulgular: Çalışmaya 131 aile hekimi katılmış olup, erkek katılımcı oranı daha yüksek bulunmuştur. Sigara içme sıklığının Türk aile hekimleri arasında anlamlı derecede yüksek olduğu tespit edilmiştir (p=0,013). Ancak, ölçek toplam puanı veya altı boyutta alınan puanlar açısından aile hekimleri arasında istatistiksel olarak anlamlı bir fark bulunmamıştır.

Sonuç: Çoğu aile hekimi, bu alanda daha fazla eğitim almak istediklerini belirtmiştir, bu da tıp fakültelerinin müfredatına eğitim müdahalelerin dahil edilmesi gerekliliğini göstermektedir. Ayrıca, iyi yapılandırılmış web tabanlı kitlesel çevrimiçi kurslar, aile hekimlerinin sağlıklı yaşam biçimi davranışları ve yaşam biçimi tıbbı uygulamalarına yönelik eğitim gereksinimlerini karşılamada etkili bir çözüm olabilir.

Anahtar Sözcükler: Yaşam biçimi tıbbı, aile hekimliği, klinik uygulama

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Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

INTRODUCTION

In 1989, a new approach, "lifestyle medicine (LSM)," entered the field of medicine during a symposium on cancer (1). Rippe has published an article that indicates the association between lifestyle and risk factors of chronic diseases in his book (2). While lifestyle modifications can improve health status, many guidelines and institutions also brought LSM to the forefront (2-4).

LSM is a growing field and is defined in the Journal of the American Medical Association as "evidence-based practice of assisting individuals and their families to adopt and sustain behaviors that can improve health and quality of life" (5,6). Nowadays, LSM is essential not only for patients who struggle with non-communicable diseases but also for primary care physicians, whose duties include managing and preventing non-communicable diseases. Medical doctors, who are role models in their society, have particularly important awareness and attitudes, especially those of family physicians (FPs), due to their holistic, patient-centered, and person-involved approach (7). Furthermore, LSM practices can reduce healthcare costs by decreasing the need for medications, procedures, and hospitalizations (8). Primary care physicians who learn LSM practices can provide patients with evidence-based recommendations that are tailored to their individual needs and preferences. They can also offer ongoing support and education to help patients make sustainable lifestyle changes (9).

Well-structured goals for LSM continuing medical education for FPs include competencies in the areas of leadership, knowledge, assessment skills, management skills, and the use of office and community support (10). Patients' health behaviors and physicians' personal health behaviors are related. Increasing the use of health promotion counseling in practice requires addressing the physicians' own health practices, which are strongly and consistently related to health promotion counseling. Patients also find doctors who briefly describe some of their own healthier habits to be more credible and inspiring (11,12). If a LSM approach could be internalized in primary care, which is responsible for the management of non-communicable diseases, the causes of these diseases could be restrained (10,12). Patients' behaviors could be our target for improvement, while the well-being of health workers is also crucial. The priority should be implementing the healthcare system (13).

MATERIALS AND METHODS

Data collection for this study primarily relied on a questionnaire. The questionnaire consisted of two sections designed to gather relevant information from the participants. The first section, developed by reviewing the relevant literature, aimed to collect personal information, including demographic details, general health perception, habits, nutritional and physical activity status, as well as inquiries about the participants' engagement in LSM practices within their clinical practice.

To assess healthy lifestyle behaviors, the Healthy Lifestyle Behavior Scale-II, developed by Walker, Sechrist, and Pender (1987) and revised in 1996 (14), is used. was utilized. The scale, previously tested for reliability and validity in a Turkish context by Pınar et al. (12), comprised 52 items and six sub-scales: health responsibility, physical activity, nutrition, moral development, interpersonal relations, and stress management (16).

The internet-based questionnaire was created using Google Docs and distributed via email, social media platforms, and WhatsApp to FPs groups between July 2018 and August 2019. The questionnaire was provided in both English and Turkish to accommodate the participants' language preferences.

Ethical approval for the study was obtained from the Ethical Committee of İzmir University of Economics (Approval number: 11, date: 04.09.2018). Informed consent was obtained individually from each participant at the beginning of the survey. Participants provided digital consent for participation, and data collected during the study were securely stored on an encrypted hard drive by the principal investigator. Prior to distribution, the electronic questionnaire (in English) was pilot tested to ensure clarity and ease of use. The survey was open to the public, and participants were recruited through various online channels, including social media and email groups. Responses were directly entered into a database, and survey completion was voluntary, with no incentives provided. The questions were formatted in the Google form, allowing the investigators to easily check for completeness of responses.

The collected data were analyzed using SPSS version 21 (IBM, Chicago, IL, USA). Descriptive statistics, correlational analyses, and group comparison analyses were performed. Non-parametric tests such as Spearman rho, Mann-Whitney U, and Kruskal-Wallis H were employed to accommodate the non-normal distribution of the data.

RESULTS

Participants were 131 FPs, 64 of whom were Turkish native speakers. The male gender ratio was higher, with (88) males. These FPs were from the special interest groups, and only 10% didn't answer as they were "busy" and/or "on vacation."

The frequency of smoking is statistically significant higher in the Turkish FPs (p=0.013).

Compared to the Turkish FPs' group, the non-Turkish FPs were statistically significantly higher in terms of age (p=0.002) and average years worked in family health center (FHC) (p=0.001).

The frequency of female sex in the Turkish physician group was statistically significantly higher (p=0.024). The frequency of smoking was statistically significantly higher in the Turkish FPs group (p=0.013). No statistically significant difference was observed between female and male participants in the whole study group regarding the total scale score and the scores of six dimensions. (Table 1).

No statistically significant difference was observed in the overall study group for the total scale total score and six-dimension scores according to cigarette/e-cigarette use. (Table 2).

Table 3 shows the evaluation of the characteristics of FPs' lifestyle practices and engagement with LSM.

There is a low-level positive relationship between age and nutrition. r (131)=0.18, p<0.05 (Table 4).

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

Table 1. Comparison of total scores by gender and scores of six dimensions in the whole study group

	Gender	N	Mean	Standard deviation	p
Scale total score	Male	88	18.6364	5.41429	0.323
	Female	43	17.6429	5.18356	
Health responsibility	Male	88	21.4318	4.20125	0.290
	Female	43	20.5000	5.54912	
Stress management	Male	88	16.5568	3.97942	0.240
	Female	43	15.7381	3.01265	
Self-improvement	Male	88	28.9318	5.48309	0.389
	Female	43	28.0000	6.28199	
Interpersonal relationships	Male	88	26.0795	4.48297	0.128
	Female	43	24.7381	5.05607	
Nutrition	Male	88	23.3977	4.79113	0.833
	Female	43	23.2143	4.22268	
Physical activity	Male	88	18.6364	5.41429	0.323
	Female	43	17.6429	5.18356	

t test in independent groups

Table 2. Comparison in terms of total score and six dimensions according to cigarette/e-cigarette use in the whole study group

	Cigarette/e-cigarette use	n	Mean	Standard deviation	p
Scale total score	Yes	9	133.2222	20.00486	0.323
	No	122	133.1393	22.29714	
Health responsibility	Yes	9	20.1111	3.48010	0.290
	No	122	21.1393	4.79551	
Stress management	Yes	9	17.3333	2.29129	0.240
	No	122	16.2049	3.76793	
Self-improvement	Yes	9	28.1111	5.84047	0.805
	No	122	28.6066	5.77907	
Interpersonal relationships	Yes	9	27.2222	4.02423	0.300
	No	122	25.5410	4.72053	
Nutrition	Yes	9	23.3333	4.63681	0.989
	No	122	23.3115	4.60701	
Physical activity	Yes	9	17.1111	5.27836	0.511
	No	122	18.3361	5.38840	

t test in independent groups

There is a significant but low-level negative relationship between graduation year and nutrition. r (131) =0.20, p<0.05. (Table 5)

When the averages are considered, the waist/hip ratio of men (M=0.96, SE=0.02) is higher than that of women (M=0.79, SE=0.22). The difference between them is significant. t (100) =4.674, p<0.05 (Table 6).

The Body Mass Index (BMI) of women (M=23.39, SE=0.48) is lower than that of men (M=26.96, SE=0.88). The difference between them is significant. t (128) =-3.849, p<0.05

FPs reported that the origin of the LSM knowledge was their curriculum of the trainee program and/or faculty of medicine (37.4%-19.1%), while 42.7% have learned by themselves due to their special interest. The most needed subjects in which improvement was needed were stress management, nutrition, physical activity, healthy sexual life, and smoking addiction.

Most of the participants were willing to improve their knowledge about LSM (96.2%), and 84% of FPs were using LSM for their daily practice. 71% of the FPs have assessed their patients' compliance to lifestyle modification as more than medium.

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

Table 3. Characteristics of FPs' lifestyle practices and engagement with lifestyle medicine

			Do you recommend lifestyle changes in the prevention and treatment of diseases to your patients?			Total
			Always	**Usually**	**Sometimes**	
Do you use tobacco products containing nicotine such as cigarettes/electronic cigarettes / waterpipe?	Yes	n	6	2	1	9
		Percentage	66.7%	22.2%	11.1%	100.0%
	No	n	80	34	8	122
		Percentage	65.6%	27.9%	6.6%	100.0%
Do you track the calories you get daily?	Always	n	3	0	0	3
		Percentage	100.0%	0.0%	0.0%	100.0%
	Usually	n	26	3	1	30
		Percentage	86.7%	10.0%	3.3%	100.0%
	Sometimes	n	29	16	1	46
		Percentage	63.0%	34.8%	2.2%	100.0%
	Rarely	n	10	13	3	26
		Percentage	38.5%	50.0%	11.5%	100.0%
	Never	n	18	4	4	26
		Percentage	69.2%	15.4%	15.4%	100.0%
Do you add salt without tasting food?	Always	n	2	0	0	2
		Percentage	100.0%	0.0%	0.0%	100.0%
	Usually	n	4	0	3	7
		Percentage	57.1%	0.0%	42.9%	100.0%
	Sometimes	n	17	8	1	26
		Percentage	65.4%	30.8%	3.8%	100.0%
	Rarely	n	16	9	3	28
		Percentage	57.1%	32.1%	10.7%	100.0%
	Never	n	47	19	2	68
		Percentage	69.1%	27.9%	2.9%	100.0%

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

Table 3. Characteristics of FPs' lifestyle practices and engagement with lifestyle medicine

			Do you recommend lifestyle changes in the prevention and treatment of diseases to your patients?			Total
			Always	Usually	Sometimes	
How many cups (1 glass=200 ml) of carbonated beverages (Cola, Fanta, Sprite, etc.) do you drink in a week?	Never	n	45	16	5	66
		Percentage	68.2%	24.2%	7.6%	100.0%
	1-2 glasses	n	31	13	2	46
		Percentage	67.4%	28.3%	4.3%	100.0%
	3-5 glasses	n	7	4	2	13
		Percentage	53.8%	30.8%	15.4%	100.0%
	5+ glasses	n	3	3	0	6
		Percentage	50.0%	50.0%	0.0%	100.0%
Do you use assistive mobile applications (such as iphone health, nike running club or fitnesspal) while exercising?	Always	n	8	1	0	9
		Percentage	88.9%	11.1%	0.0%	100.0%
	Usually	n	16	5	0	21
		Percentage	76.2%	23.8%	0.0%	100.0%
	Sometimes	n	23	5	2	30
		Percentage	76.7%	16.7%	6.7%	100.0%
	Rarely	n	19	8	2	29
		Percentage	65.5%	27.6%	6.9%	100.0%
	Never	n	20	17	5	42
		Percentage	47.6%	40.5%	11.9%	100.0%
Do you engage in physical activity during your daily work? (For example, to walk to work or prefer stairs instead of an elevator)	Always	n	20	2	1	23
		Percentage	87.0%	8.7%	4.3%	100.0%
	Usually	n	39	11	3	53
		Percentage	73.6%	20.8%	5.7%	100.0%
	Sometimes	n	16	15	3	34
		Percentage	47.1%	44.1%	8.8%	100.0%
	Rarely	n	9	8	2	19
		Percentage	47.4%	42.1%	10.5%	100.0%
	Never	n	2	0	0	2
		Percentage	100.0%	0.0%	0.0%	100.0%

FPs: Family physicians

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

DISCUSSION

In this study, we examined the lifestyle and practice of LSM among FPs, with a focus on the differences observed among Turkish native speakers and non-Turkish FPs. Our findings provide insights into the association between FPs' lifestyle choices and their approach to recommending lifestyle changes for patients. The World Health Organization (WHO) reports that cardiovascular diseases (CVD) are the leading cause of death globally (17). Coronary artery disease (CAD) is a major cause of CVD-related deaths. Among the risk factors found in, approximately 90%, of patients with CAD, smoking, sedentary life, excess weight and obesity, hypertension (HT), hyperlipidemia, and diabetes mellitus (DM) can be listed (18). Lifestyle changes can also be used to prevent complications related to cerebrovascular diseases, DM, and HT (19,20). For this reason, primary and secondary protection may benefit both in an individual and a social sense through lifestyle changes.

Lifestyle Medicine

The use of evidence-based lifestyle changes approaches to prevent, treat, and often reverse the main causes of chronic disease associated with lifestyle (11,21).

Table 4. Relation between nutrition and FPs' ages

		Nutrition	Age
Nutrition	Pearson correlation	1	0.182*
	Sig. (2-tailed)		0.038
	n	131	131
Age	Pearson correlation	0.182*	1
	Sig. (2-tailed)	0.038	
	n	131	131

*p < 0.05 is statically significant

Table 5. Relation between nutrition and the year of graduation

		Nutrition	Year of graduation
Nutrition	Pearson correlation	1	-0.199*
	Sig. (2-tailed)		0.023
	N	131	131
Year of graduation	Pearson correlation	-0.199*	1
	Sig. (2-tailed)	0.023	
	N	131	131

*p < 0.05 is statically significant

In this context, this research evaluates the healthy lifestyles of FPs serving in primary care and determines the place of lifestyle changes in clinical practice. No significant difference was observed in female and male gender or using neither cigarette non-e-cigarettes in the whole study group in terms of scale total score and scores of six dimensions, while there was no statistically significant difference between the Turkish and non-Turkish groups. As non-communicable diseases are universal, LSM must also be considered universally applicable.

The demographic characteristics of our participants revealed that the majority of FPs were male, with a higher proportion among the Turkish native speakers. Moreover, the Turkish FPs showed a statistically significantly higher frequency of smoking compared to the non-Turkish FPs. This observation highlights a potential area of concern for the Turkish physician group, as smoking is known to have detrimental effects on health.

Nevertheless, the frequency of smoking is statistically significant in the Turkish FPs' group compared to the non-Turkish FPs' group (p=0.013). Cigarette smoking is a cause of preventable diseases and one of the most important health problems in the world. Turkey is second in cigarette consumption per person among European countries (after Greece). It was the fifth largest production in 1997 (22). The first anti-tobacco law was adopted in 1996, and in collaboration with the WHO Framework Convention on Tobacco Control, this law has been revised in 2004 and 2008. In this way, the improvement of indoor air quality can be achieved (23). According to the Global Adult Tobacco Surveys conducted in 2008 and 2012, the prevalence of tobacco usage in Türkiye has decreased from 31.2% to 27.1%. In males, the rate has decreased from 47.9% to 41.5%, while in females, it has decreased from 15.2% to 3.1%. in another study that was carried out, the prevalence of tobacco usage was examined. However, there was a decrease between the years 2003 and 2012 followed by a resurgence in 2014 (24). As a result of the change in the law in 2008, the policy has been implemented more comprehensively. Turkey has become one of the first countries to start and complete the MPOWER criteria. However, in 2025, it is estimated that there will be about 19% of the population (around 12.7 million) as consumers. According to Çerçi's research that was performed among 415 FPs via stratified sampling in Turkey, the prevalence of smoking was revealed to be 30.9% in 2017 (25). In Atayoğlu et al. study; among 237 physicians, 58.4% of them reported as "never smoker" while 21.1% were "current smoker" and 20.5% were "former smokers" (26). In our study, the LSM approach in the daily routine of FPs was significant, and also most of them were not smoking.

FPs reported that the origin of the LSM knowledge was their curriculum of the trainee program and/or faculty of medicine

Table 6. Waist/Hip and BMI Comparison by Gender

	Group	n	Mean	SD	SE	T	df	p
Waist/Hip	Woman	88	0.79	0.19	0.022	-4.674	100	**0.00**
	Man	43	0.96	0.11	0.021			
BMI	Woman	88	23.39	4.50	0.480	-3.849	128	**0.00**
	Man	43	26.96	5.76	0.889			

BMI: Body Mass Index, SD: Standard deviation, SE: Standard Error

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

(37.4%-19.1%) while 42.7% has learned by themselves due to their special interest. Nowadays, massive open online courses (MOOCs) are gaining attention for providing access to knowledge without borders, discrimination, etc. (27). The most needed learning topics to improve themselves were stress management, nutrition, physical activity, healthy sexual life, and smoking addiction. According to Polak et al. (7) study, learning LSM improves the lifestyle of FPs, too. While the targets are well-defined, implementing these topics (especially "nutrition" and "stress-management") the curriculum seems essential not only for the trainee programs but also for future physicians.

Most of the participants were willing to improve their knowledge about LSM (96,2%), and 84% of FPs was using LSM for their daily practice. They have assessed the compliance of their patients to lifestyle modification as more than medium by 71% of the FPs. Lianov and Johnson (18) revealed that if physicians' inadequate confidence and lack of knowledge and skill could be overcome, counseling could be more successful, as changing unhealthy behaviors is a foundational aspect (21).

According to Malatskey et al. (10) "trained residents had a better awareness of LSM and were more confident in their ability to succeed and influence a patient's behavioral changes." However, participation in the LSM training was not found to be a significant predictor of either the mean composite attitude or confidence score in the multivariate linear regression models. Personal health behaviors (such as following a Mediterranean diet) and finishing medical school in Israel were discovered to be significant predictors of both the mean composite attitude and confidence scores. In our study, there wasn't any significant difference among dimensions, attitude, behavior regarding counselling on LSM (supplement). However, there is a significant relationship between age, graduation duration, and nutrition.

Burnout and lack of personal rights are some of the burdens that FPs faced over the past years (28,29). Needs of healthcare facilities include physicians counseling patients on non-communicable diseases (NCDs) prevention and treatment for primary care, especially during the COVID-19 pandemic (8,30,31). LSM could be a solution for the well-being of FPs and societies, especially in terms of nutrition and stress-management for old and new challenges of the healthcare system. Well-structured mobile applications are also valuable tools to manage LSM modifications (32).

In terms of age and years worked in a FHC, the non-Turkish FPs were significantly older and had more years of experience than their Turkish counterparts. These findings suggest a potential difference in the career trajectories between the two groups, with the non-Turkish FPs having a longer professional history. This difference may influence their approach to LSM and patient care.

Regarding gender, our results indicated a statistically significant higher frequency of female FPs among the Turkish physician group. However, no significant differences were observed between male and female FPs in terms of the total score of the overall scale and the scores of six dimensions, indicating that gender did not significantly impact the FPs' lifestyle choices and practice of LSM.

Our study, analyzing the association between lifestyle choices and the practice of LSM, found no statistically significant differences in the overall study group in terms of scale total score and scores of six dimensions according to cigarette/e-cigarette use. This suggests that the FPs' personal smoking habits did not significantly affect their adherence to a healthy lifestyle or their recommendation of lifestyle changes to patients.

Furthermore, we explored the association between FPs' lifestyle choices and specific practices related to LSM. The results showed interesting patterns. For instance, FPs who always recommended lifestyle changes to patients were more likely to track their daily calorie intake. Additionally, those who engaged in physical activity during their daily work were more likely to recommend lifestyle changes. These findings indicate a positive association between FPs' personal lifestyle choices and their commitment to promoting lifestyle changes in patient care.

Moreover, we examined the relationship between nutrition and FPs' age and year of graduation. Our analysis revealed a statistically significant but weak positive correlation between age and nutrition, suggesting that older FPs may exhibit better nutrition habits. Additionally, a negative correlation was found between nutrition and the year of graduation, indicating that FPs who graduated more recently had poorer nutritional habits. These findings underscore the importance of considering FPs' age and years of experience when addressing their nutrition practices.

Overall, our study sheds light on the lifestyle choices and practices of LSM among FPs, with specific attention to differences between Turkish native speakers and non-Turkish FPs. The results highlight the need for targeted interventions, particularly regarding smoking cessation among Turkish FPs, as well as the importance of considering FPs' age and years of experience in promoting healthy nutrition habits. These findings can inform future strategies to enhance LSM practices among FPs, ultimately benefiting patient care and overall public health.

Study Limitations

This research has been performed among the special interest groups, so they are already ready to learn and make a difference for themselves and for their communities.

CONCLUSION

LSM is universal; the concept is not affected by age, sex, cultural background, years that were spent at FHC, and also the lifestyle of FPs. The educational needs could be implemented into the curriculum of medical faculties, and well-structured, web-based MOOCs could provide a solution.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethical Committee of İzmir University of Economics (Approval number: 11, date: 04.09.2018).

Gazi Med J 2025;36(2):144-151

Gökdemir et al. Family Physicians and Lifestyle Medicine in Their Clinical Practice

Informed Consent: Informed consent was obtained individually from each participant at the beginning of the survey.

Footnotes

Authorship Contributions

Concept: Ö.G., H.K., Design: Ö.G., H.K., Supervision: M.İ.Ş., Resources: Ö.G., H.K., Material: Ö.G., H.K., Data Collection or Processing: Ö.G., H.K., M.İ.Ş., Analysis or Interpretation: Ö.G., H.K., M.İ.Ş., Literature Search: Ö.G., H.K., Writing: Ö.G., H.K., M.İ.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Dual Therapy with Ellagic Acid and Carnosic Acid Ameliorates STZ-Induced Diabetic Conditions in Rats by Alleviating Liver Oxidative Stress

Elajik Asit ve Karnosik Asit ile Yapılan İkili Tedavi Karaciğer Oksidatif Stresini Hafifleterek Sıçanlarda STZ ile İndüklenen Diyabetik Koşulları İyileştirir

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ABSTRACT

Objective: Diabetes, a significant public health issue today, causes serious health problems due to its complications and will become a global epidemic if no action is taken. Diabetic patients experience elevated oxidative stress, which impairs wound healing. The purpose of this study was to investigate the effects of ellagic acid (EA) and carnosic acid (CA) on oxidative events in liver tissue in diabetic rats with wounds.

Methods: The rats were divided into 7 groups as control, untreated-3 day, untreated-7 day, topical-3 day, topical-7 day, oral-3 day and oral-7 day. To induce diabetes in the subjects, each group received a single intraperitoneal injection of streptozotocin. Rats were treated topically or orally with EA + CA. On the 3rd and 7th days of recovery, the rats were sacrificed and the levels of nitric oxide (NOx), malondialdehyde (MDA), glutathione (GSH), protein carbonyls (PC), and ascorbic acid (AA) were measured spectrophotometrically to investigate the effects of oxidative stress in liver tissue.

Results: Liver tissue MDA, NOx, and PC levels were determined to be statistically decreased in both topical and oral applications compared to the control and untreated groups (p<0.05). Liver tissue GSH, AA, and collagen levels were found to be statistically increased in both topical and oral applications when compared to the control and untreated groups (p<0.05).

Conclusion: These results show that the combination of EA and CA with two different application methods significantly reduces oxidative

ÖZ

Amaç: Önemli bir halk sağlığı sorunu haline gelen diyabet, komplikasyonlarıyla birlikte ciddi sağlık sorunları oluşturmakta ve önlem alınmaz ise küresel bir salgın şeklinde ilerlemektedir. Diyabetik hastalarda oksidatif stres artmakta ve yara iyileşmesi bozulmaktadır. Bu çalışmanın amacı, yaralı diyabetik sıçanlarda elajik asit (EA) ve karnosik asidin (CA) karaciğer dokusundaki oksidatif olaylar üzerindeki etkilerini araştırmaktır.

Yöntemler: Sıçanlar kontrol, tedavisiz-3 gün, tedavisiz-7 gün, topikal-3 gün, topikal-7 gün, oral-3 gün ve oral-7 gün olmak üzere 7 gruba ayrıldı. Tüm gruplara diyabet modeli oluşturmak amacıyla tek doz streptozotosin enjekte edildi. Sıçanlar EA + CA ile topikal veya oral olarak tedavi edilmiştir. İyileşmenin 3. ve 7. günlerinde sıçanlar sakrifiye edilmiş ve karaciğer dokusunda oksidatif stresin etkilerini araştırmak için nitrik oksit (NOx), malondialdehit (MDA), glutatyon (GSH), protein karbonilleri (PC), askorbik asit (AA) seviyeleri spektrofotometrik olarak ölçülmüştür.

Bulgular: Karaciğer dokusu MDA, NOx ve PC düzeyleri hem topikal hem de oral uygulamalarda kontrol ve tedavisiz gruplara kıyasla istatistiksel olarak düşük bulundu (p<0,05). Karaciğer dokusu GSH, AA ve kollajen düzeyleri hem topikal hem de oral uygulamalarda kontrol ve tedavisiz gruplara kıyasla istatistiksel olarak yüksek bulundu (p<0,05).

Sonuç: Bu sonuçlar, EA ve CA'nın iki farklı uygulama yöntemiyle kombinasyonunun karaciğer dokusundaki oksidatif olaylara etki ederek ilaç metabolizmasındaki oksidatif stresi önemli ölçüde azalttığını ve

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Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

ABSTRACT

stress associated with drug metabolism by affecting oxidative events in liver tissue, and has the potential to prevent possible complications of diabetes.

Keywords: Ellagic acid, carnosic acid, oxidative stress, liver, inflammation

ÖZ

diyabetin olası komplikasyonlarını önleme konusunda potansiyeli olduğunu göstermektedir.

Anahtar Sözcükler: Elajik asit, karnosik asit, oksidatif stres, karaciğer, enflamasyon

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic endocrine disorder that affects carbohydrate, protein, and lipid metabolism due to insufficient or absent insulin secretion and/or action (1). Recent data published by the International Diabetes Federation shows that there are approximately 9 million people with diabetes in Türkiye between the ages of 20-79 years, which represents approximately 14.5% of the total adult population (2). All types of diabetes are linked to the dysfunction and destruction of beta cells. Factors such as autoimmunity, inflammation, insulin resistance, obesity, an aging population, and physical inactivity can lead to the loss of pancreatic beta cells (1).

Uncontrolled diabetes can lead to various macrovascular complications, including macrovascular complications such as coronary artery disease, and microvascular complications such as neuropathy, nephropathy, and retinopathy. These complications occur in the long term due to oxidative stress caused by increased reactive oxygen species (ROS) production (3). Additionally, diabetes can impair wound healing due to infection, local circulatory disturbance caused by angiopathy, and peripheral neuropathy. The cause of diabetic wounds is not certain, but it may be due to accelerated atherosclerosis and infections induced by decreased perfusion, caused by neuropathy, slow collagen synthesis and deposition, decreased angiogenesis, and weaker tensile strength of the wound (4). As normal wound healing cannot occur, free radicals or oxidants continue to increase tissue damage by targeting DNA, proteins, and lipids (5,6). Biological systems have an integrated antioxidant defence system, including catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD), to counteract these molecules (7).

Patients are cautious about the use of medications to treat diabetic wounds because of the potential negative metabolic effects of the drugs. As the principal organ for drug metabolism, the liver is essential to drug detoxification and the body's removal of chemicals. The genesis of drug-induced hepatotoxicity is an early event that generates radical species, such as ROS (8). Additionally, it contains a higher concentration of antioxidant enzymes such as CAT and glutathione peroxidase than other organs (9).

Endogenous and exogenous drugs, as well as specialised devices and techniques, are used to treat diabetic wounds. However, due to the low success rate of treatment, high cost, and potential side effects to the patient, as well as an increase in oxidative stress during the process, late wound closure or organ loss may occur. Therefore, the use of compounds with natural antioxidant content is necessary in the treatment of impaired wounds. According to the data gathered, ellagic acid (EA) and carnosic acid (CA) have properties that can prevent or treat a variety of diseases, including diabetes, Parkinson's disease, cancer, cardiovascular disease, ulcerative colitis, and Alzheimer's disease. These properties include anti-inflammatory, antioxidant, and antimicrobial effects (10-14). EA exhibits anti-inflammatory activity by reducing mediator molecules such as interleukin-6 and tumour necrosis factor-α. Additionally, it scavenges free radicals through transcriptional activation of nuclear erythroid 2-related factor 2 (Nrf2) and has antioxidant activity against toxic conditions in the liver (12,13). CA is another compound that exhibits antioxidant efficacy by disrupting the formation of the Nox4 enzyme complex through inhibition of the nuclear factor-kappa B (NF-κB) inhibitor signaling pathway (14). It acts as a metal ion chelator and is a potent scavenger of peroxyl radicals. Its effect on membrane lipid peroxidation is higher than that reported for artificial antioxidants (15,16). CA has been demonstrated to protect against lipopolysaccharide-induced liver injury by inducing phase 2 antioxidant enzymes. Moreover, it reduces oxidative/nitrosative stress caused by lipopolysaccharide (LPS) by reducing lipid peroxidation, serum nitric oxide (NOx) levels, and protein carbonylation (17). In combination with other natural compounds, CA has shown beneficial effects in most experimental disease models and is a promising compound in many fields (11,17).

This study hypothesizes that the administration of these two compounds can significantly impact oxidative stress in drug metabolism. To this end, the effects of various routes of administration of EA and CA on oxidative stress in liver tissue were evaluated for the first time.

MATERIAL AND METHODS

Animals

The Gazi University Laboratory Animal Committee Ethics Committee granted permission for the investigations (approval number: G.U.ET-20.012, date: 14.02.2022). Prior to tissue sample collection, all procedures were carried out at the Animal Breeding and Experimental Research Center (GUDAM) of Gazi University Laboratory. Forty-two male albino Wistar rats weighing 250-300 g were used, and these were utilized in the studies from GUDAM. The rats were fed freely both before and throughout the experiment, and they were housed in separate cages at 20±5 °C with synchronized light cycles.

Creation of a Diabetes and Wound Model

To develop diabetes, rats were given a single dose of 60 mg/kg streptozotocin intraperitoneally (Sigma-Aldrich). After three days, blood glucose levels were tested, and those greater than 250 mg/dL were classified as diabetic. The animals were weighed, and

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

anaesthetised according to their weight. Intramuscular injections of ketamine (Alfasan, NED 50 mg/kg) and xylazine (Alfasan, NED 5 mg/kg) were administered to induce anaesthesia. Following anaesthesia, the dorsal region of the animals was shaved without damaging the skin. The animals were then restrained face down. With the exception of the control group, six full-thickness excisional wounds were created on both sides of the spine in parallel, in the dorsal region of all animals using a punch biopsy (Acuderm, USA).

Experimental Design and Liver Tissue Collection

The rats were divided into seven groups, as shown in Table 1: control; untreated-3 day; untreated-7 day; topical-3 day; topical-7 day; oral-3 day and oral-7 day.

The topical gel was prepared using Carbopol 974P at a concentration of 2%. CA was dispersed in distilled water (98 g) and mixed at 800 rpm for 60 minutes. A 10% NaOH solution was added dropwise to this mixture to form a transparent gel (18). The dose of EA and CA was adjusted to 10 mg/kg. The gel was stored at +4 °C for 24 hours to eliminate air bubbles. It was then UV sterilised and prepared for *in vivo* topical application. The gel formulation, which contained EA + CA, was spread as a thin layer on a Petri dish and sterilised under a 254 nm UV-C lamp in a laminar flow cabinet for 2 hours. In the topical administration groups, a single daily dose of EA + CA (10 mg/kg), containing gel, was applied topically to each wound. In the oral administration groups, a single daily dose of EA + CA (10 mg/kg) was administered by oral gavage after being dissolved in water.

The experiment weighed the animals on a standard balance and induced general anaesthesia by injecting them with ketamine (alfamine 50 mg/kg) and xylazine (alfazyne 5 mg/kg) in proportion to their weight. Spectrophotometric evaluation was used to measure the levels of malondialdehyde (MDA), GSH, NOx, protein carbonyls (PC), ascorbic acid (AA), and collagen in the liver tissue of the sacrificed animals on days 3 and 7.

Biochemical Analysis

MDA, GSH, NO and AA Determination

The Buege and Aust (19) method was utilized. A homogenizer set at 5000 rpm was used to homogenize liver tissue in 150 mM KCl. The tissue sample was mixed with 15% TCA solution to precipitate the protein. After centrifuging the precipitate, a portion of the supernatant was combined with 0.67% TBA and 1% BHT, and the mixture was heated. The spectrophotometer was used to measure absorbance at 532 nm after cooling.

The Elman method was used to measure GSH levels in tissue samples. The samples were homogenized in 0.15 M cold KCl, and then to deproteinize the homogenate, a metaphosphoric acid-EDTA NaCl combination was added. DTNB solution was added to the 0.3 M Na_2HPO_4 supernatant following centrifugation. The samples were measured at 412 nm (20).

The AA determination procedure in tissue involves homogenizing the tissues in a cold PCA/EDTA combination, as described by Roe and Kutherin and as further edited by Berger et al. (21). Next, the homogenate was centrifuged. Two tubes were prepared: one carrying a conventional AA solution and the other containing PCA solution. The samples were then prepared in the tubes holding the supernatant and incubated individually after a color reagent was added. The samples were mixed and sulfuric acid was added to each tube. Then, the mixture was maintained at room temperature. Spectrophotometry was used to analyze the samples at a wavelength of 520 nm.

The NOx level in the tissue was evaluated by detecting the stable end products, nitrite and nitrate, using the Griess reaction. To deproteinize the sample, 0.3 M NaOH and 10% $ZnSO_4$ were used. After the experiment, the mixture was centrifuged, and the supernatants were employed in the Griess experiment (22).

Assay Methods of PC and Collagen

Reznick and Packer (23) developed a method for measuring the amount of reactive carbonyl groups in protein oxidation, which indicates the existence of oxidative stress. We employed the hydrazone formation method to measure the PC groups, where hydrazone is produced by the interaction of 2,4-dinitrophenylhydrazine with protein carbonyl groups. We next examined the PC groups spectrophotometrically at 370 nm and calculated the total protein content at 280 nm (24). The modified Lowry method (25) was used to measure collagen concentrations in tissues.

Statistical Analysis

For all values, the arithmetic mean ± standard error was used. One-way ANOVA and the Tukey's multiple comparison test were used to

Table 1. Group specifications

Groups	Specifications
Control	STZ injected, not wounded, no treatment (n=6).
Untreated 3 day	STZ injected, wounded, no treatment, sacrificed at post wounding day 3 (n=6).
Untreated 7 day	STZ injected, wounded, no treatment, sacrificed at post wounding day 7 (n=6).
Topical 3 day	STZ injected, wounded, a single daily dose EA + CA (10 mg/kg) was applied topically to wounds, sacrificed at post wounding day 3 (n=6).
Topical 7 day	STZ injected, wounded, a single daily dose EA + CA (10 mg/kg) was applied topically to wounds, sacrificed at post wounding day 7 (n=6).
Oral 3 day	STZ injected, wounded, a single daily dose EA + CA (10 mg/kg) was applied orally, sacrificed at post wounding day 3 (n=6).
Oral 7 day	STZ injected, wounded, a single daily dose EA + CA (10 mg/kg) was applied orally, sacrificed at post wounding day 7 (n=6).

STZ: Streptozotocin, EA: Ellagic acid, CA: Carnosic acid.

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

assess the values (SPSS 16.0 for Windows, SPSS Inc., USA). P values less than 0.05 were regarded as statistically significant.

RESULTS

MDA Levels of Groups

The MDA levels in the liver tissue of the various groups are displayed in Figure 1 and Table 2. MDA levels were significantly lower in the oral and topical application groups than in the control and untreated groups (p<0.05). Because of enhanced lipid peroxidation, the liver MDA levels were greater in the untreated groups observed at 3 and 7 days.

GSH Levels of Groups

Liver tissue GSH levels were significantly higher in the topical and oral treatment groups compared to the control and untreated groups (Figure 2 and Table 2) (p<0.05). A significant increase was

Figure 1. MDA level in the livers of groups.

*p<0.05 compared to control, **p<0.05 compared with untreated 3 day group, ***p<0.05 compared with untreated 7 day group.

MDA: Malondialdehyde.

found in the 7-day oral treatment group when compared to the 3-day oral treatment group (p<0.05) (Figure 2). The administration of both substances, orally and topically, resulted in an increase in GSH production in liver tissue, due to their antioxidant capacity against oxidative stress. It is believed that EA and CA possess synergistic antioxidant properties. The decrease in oxidative stress occurred due to the antioxidant capacity of the compounds used in the application (EA and CA), which reduced lipid peroxidation and oxidative damage.

NOx Levels of Groups

According to the study, the untreated 3-day and 7-day diabetic groups had substantially higher NOx levels than the control group (Table 2) (p<0.05). Figure 3 shows that all oral and topical application groups had significantly lower NOx levels than the untreated groups (p<0.05). Figure 3 and Table 2 show that the 3-day oral application

Figure 2. GSH level in the livers of groups.

*p<0.05 compared to control, **p<0.05 compared with untreated 3 day group, ***p<0.05 compared with untreated 7 day group, #p<0.05 compared with topical 3 day group, ##p<0.05 compared with topical 7 day group, ###p<0.05 compared with oral 3 day group.

GSH: Glutathione.

Table 2. MDA, GSH, NOx, AA, PC and collagen levels in the liver tissue of rats

Groups	MDA (nmol/g tissue)	GSH (µmol/g tissue)	NOx (nmol/g tissue)	AA (µg/g tissue)	PC (nmol/g tissue)	Collagen (mg/g tissue)
Control	46.02±4.57	5.13±1.21	27.24±3.58	14.51±0.73	13.59±1.63	42.80±2.00
Untreated 3 day	57.29±3.60*	3.81±0.55	32.79±1.8*	8.33±0.22*	14.82±2.41	26.13±4.21*
Untreated 7 day	62.37±4.22*	4.68±1.01	35.06±3.8*	8.03±0.52*	28.38±3.52*,**	20.82±1.80*,**
Topical 3 day	16.39±3.5*,**,***	9.39±2.10*,**,***	11.39±3.30*,**,***	14.26±0.55**,***	23.52±2.54*,**,***	27.18±2.77*,***
Topical 7 day	14.83±2.03 *,**,***	11.29±1.33*,**,***	6.72±1.65*,**,***	14.13±0.41**,***	12.02±1.81***,#	31.73±1.94*,**,***,#
Oral 3 day	1.48±1.40*,**,***	9.78±1.06*,**,***	4.94±1.97*,**,***,#	11.71±0.45*,**,***,#,##	18.01±2.04*,***,#,##	30.23±1.61*,***
Oral 7 day	12.88±2.02*,**,***	12.10±0.48*,**,***,#,###	3.81±1.08*,**,***,#	14.26±2.10**,***,###	10.14±1.43**,***,#,###	34.28±1.95*,**,***,#

*p<0.05 compared to control, **p<0.05 compared with untreated 3 day group, ***p<0.05 compared with untreated 7 day group, #p<0.05 compared with topical 3 day group, ##p<0.05 compared with topical 7 day group, ###p<0.05 compared with oral 3 day group.

MDA: Malondialdehyde, GSH: Glutathione, NOx: Nitric oxide AA: Ascorbic acid, PC: Protein carbonyls.

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

group had a lower NOx level ($p<0.05$) than the 3-day non-oral application therapy group.

AA Levels of Groups

In all treated groups where EA and CA together were administered, AA levels in liver tissue were statistically higher than in the untreated groups (Figure 4) ($p<0.05$). In the groups that did not receive treatment, the AA level was significantly lower than in the control group (Table 2). The AA level was significantly higher in the 7-day oral treatment group than in the 3-day oral gavage treatment group, while it was lower in the 3-day oral treatment group compared to the 3-day topical treatment group (Figure 4) ($p<0.05$).

PC Levels of Groups

The 7-day untreated group had substantially greater PC levels compared to the control and 3-day untreated groups (Figure 5; $p<0.05$). A comparison of topical treatment groups found that the 3-day group had significantly higher PC levels than the control and

7-day groups. When compared to the untreated group, the 3-day oral therapy group considerably increased in effect, while the 7-day oral therapy group dramatically reduced in effect ($p<0.05$) (Figure 5 and Table 2).

Collagen Levels of Groups

Collagen levels in liver tissue were found to be significantly higher in all groups treated with both EA and CA than in the untreated 7-day group (Figure 6). Furthermore, a significant decrease was observed in all treatment groups, including the untreated group, when compared to the control group. There was no significant difference observed between the 3-day topical and 3-day oral groups, or between the 7-day topical and 7-day oral application groups ($p>0.05$). In all groups that were treated, both topical and oral gavage applications of EA and CA resulted in an increase in collagen levels in liver tissue (Figure 6 and Table 2).

Figure 3. NOx level in the livers of groups.

*$p<0.05$ compared to control, **$p<0.05$ compared with untreated 3 day group, ***$p<0.05$ compared with untreated 7 day group, #$p<0.05$ compared with topical 3 day group.

NOx: Nitric oxide.

Figure 5. PC level in the livers of groups.

*$p<0.05$ compared to control, **$p<0.05$ compared with untreated 3 day group, ***$p<0.05$ compared with untreated 7 day group, #$p<0.05$ compared with topical 3 day group, ##$p<0.05$ compared with topical 7 day group, ###$p<0.05$ compared with oral 3 day group

PC: Protein carbonyls.

Figure 4. AA level in the livers of groups.

*$p<0.05$ compared to control, **$p<0.05$ compared with untreated 3 day group, ***$p<0.05$ compared with untreated 7 day group, #$p<0.05$ compared with topical 3 day group, ##$p<0.05$ compared with topical 7 day group, ###$p<0.05$ compared with oral 3 day group.
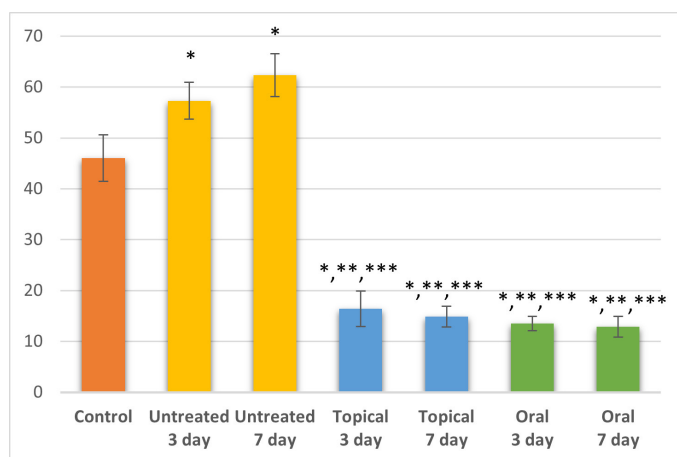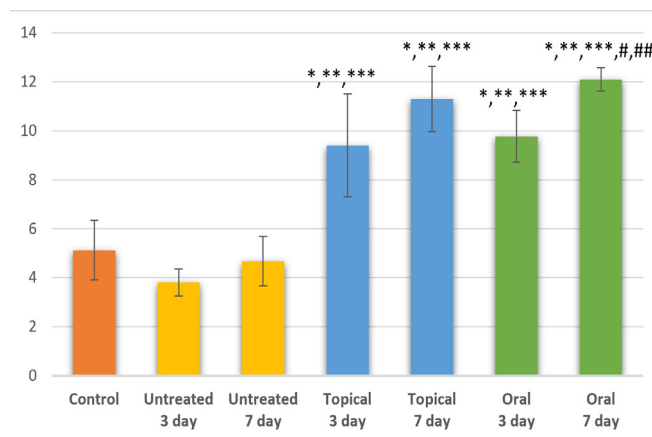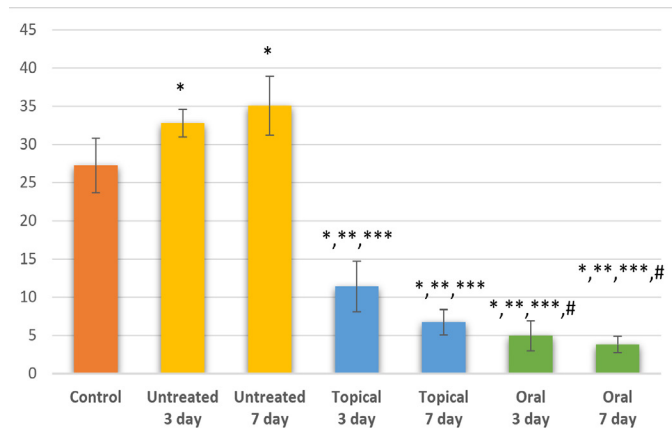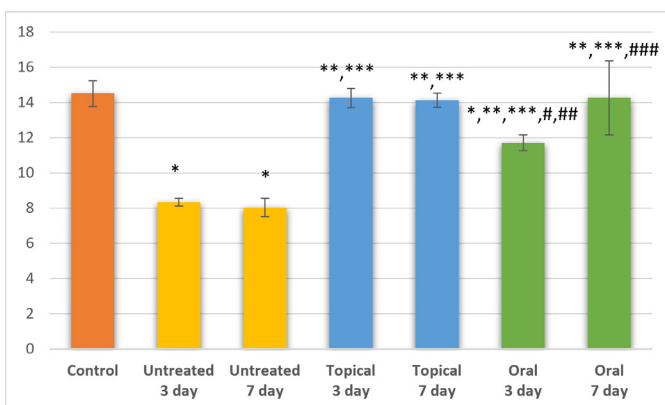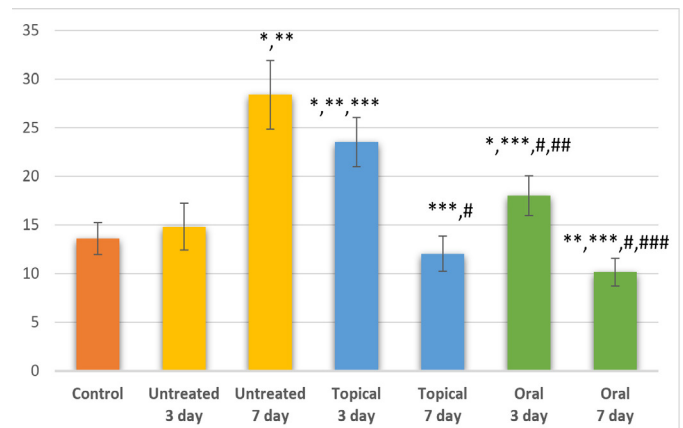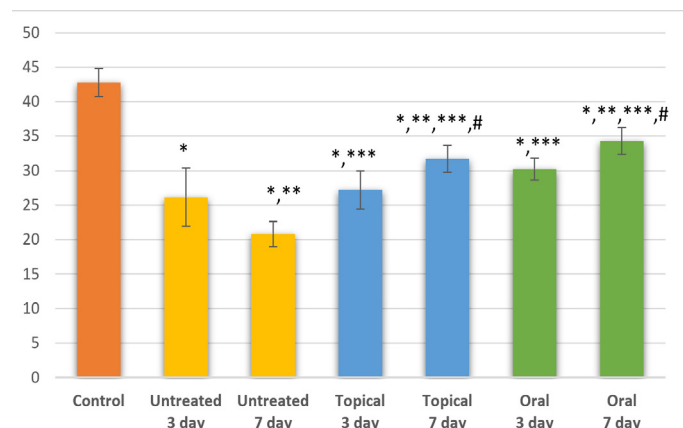

Figure 6. Collagen level in the livers of groups.

*$p<0.05$ compared to control, **$p<0.05$ compared with untreated 3 day group, ***$p<0.05$ compared with untreated 7 day group, #$p<0.05$ compared with topical 3 day group, ##$p<0.05$ compared with topical 7 day group, ###$p<0.05$ compared with oral 3 day group

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

DISCUSSION

Wound healing is a dynamic and complex process that involves hemostasis, inflammation, proliferation, and maturation phases. Local and systemic factors, such as DM, play a crucial role in wound healing. The chronicisation of diabetic wounds involves various factors, including an impaired immune system due to decreased perfusion caused by accelerated atherosclerosis and neuropathy, decreased angiogenesis, slower collagen synthesis and deposition, weaker tensile strength of wounds, and impaired oxidative balance (26). Diabetes disrupts the redox equilibrium, leading to oxidative stress brought on by either a reduction in the activity of antioxidant systems or an increase in the production of free radicals. The liver is the primary organ where specific enzymes accumulate and perform a two-stage detoxification process to scavenge free radicals (27). When diabetes and its complications are not effectively controlled, diabetic wounds can become chronic, leading to impaired oxidative balance and potentially severe consequences. Numerous studies have demonstrated the antioxidant and anti-inflammatory properties of EA and CA, which help to balance oxidative stress. This work investigates the effect of different applications of EA and CA on oxidative damage in diabetic wounds, since the liver is the most important organ for detoxification enzymes that scavenge free radicals.

Abdelkader et al. (28) carried out research on liver toxicity and found that oral gavage administration of EA had an inhibitory effect on oxidative stress. This was demonstrated by measuring liver MDA, NOx, and GSH levels. Our study also showed a significant decrease in MDA and NOx levels in the groups that received both EA and CA, indicating a reduction in oxidative stress. Although no significant difference was observed in the MDA level of the treated groups with oral and topical application, the significant decrease in NOx in the oral application groups suggests that the antioxidant effect of these two substances may be more effective in the gastrointestinal tract. Furthermore, Xiang et al. (16) discovered that the harmful effects of NOx, cytokines, and free oxygen radicals were all inhibited by CA. Furthermore, by raising liver GSH levels, it markedly improved the body's cellular antioxidant defense mechanism.

NOx is a molecule that contributes to every stage of wound healing, including angiogenesis, epithelial cell migration, keratinocyte proliferation, and collagen secretion by fibroblasts. Although it has a protective effect at physiological doses, at high levels, it exhibits a cytotoxic effect and reacts with ROS in the body to form radicals (29). The significant increase in NOx in the untreated groups and the significant decrease in NOx in the orally treated groups indicate that the two substances reduce nitrosative stress. These findings are consistent with those of Xiang et al. (16). Bagheri Tadi et al. (30) investigated the gene expression of antioxidant and oxidative stress factors in chronic wounds of diabetic rats by applying adipose-derived stem cell-associated photobiomodulation. The study found that this application strongly facilitated the inflammatory and proliferative phases of the wound healing process, by reducing the inflammatory response, NOx1, and NOx4. According to this study, the reduced NOx ratio in liver tissue resulting from the various EA and CA applications used in our study may have hastened the inflammatory and proliferative phases of wound healing processes, leading to increased formation of granulation tissue.

Enzymatic catalysis and chemical processes can both be used to create MDA from polyunsaturated fatty acids. It is one of the end products of lipid peroxidation metabolism (31). The low levels of MDA in both the oral gavage and topical treatment groups suggest that EA and CA reduce oxidative stress by decreasing lipid peroxidation in the liver. Zhu et al. (32) conducted a study on brain tissue, which showed that EA scavenges free radicals, reduces ROS production, and exhibits anti-inflammatory effects by regulating Nf-κB, MAPKs, and JAK/STAT pathways. This supports our own findings. The liver is the primary organ for harboring detoxification enzymes and the scavenging of endogenous and exogenous free radicals (8). In this study, we found no significant difference in MDA levels in liver tissue between the topical and oral-treated groups. This lack of difference may be attributed to the poor water solubility and low bioavailability of EA. In the gastrointestinal tract and other places, such as the liver, phase I and phase II enzymes metabolize EA, converting it into more water-soluble metabolites that may be eliminated in the urine or held in tissues (33). In their study on Iberian pigs, Espín et al. (34) discovered that the urolithin metabolite resulting from EA was only present in high concentrations in the gallbladder and urinary bladder, but not in any of the tested tissues, including muscle, liver, heart, and adipose tissue. The untreated groups showed that hydroxyl and peroxyl radicals were responsible for initiating and promoting lipid peroxidation, resulting in an increase in MDA. The low levels of MDA in the EA-treated and CA-treated groups may be due to EA's ability to inhibit lipid peroxidation even at very low concentrations, as demonstrated in Priyadarsini et al. (35).

Our study revealed a significant reduction in oxidative effects in liver tissue following the administration of 10 mg of EA and CA. CA was used in addition to EA due to its antioxidant and anti-inflammatory effects, which have been shown to be beneficial in treating various health disorders (10,11). Furthermore, we assessed oxidative events in the liver tissue of subjects with diabetic wounds for the first time by using both EA and CA, taking into account, the low bioavailability of EA and high bioavailability of CA (33,34,36). In a recent work by Chen et al. (36), the distribution of CA in various tissues, including the liver, stomach, and digestive contents, was determined to investigate its absorption and transport mechanisms. The researchers concluded that CA is both locally and systemically accessible in the digestive tract after it was administered orally for seven days. Additionally, the study raises the possibility that the gut microbiota is essential for the breakdown and assimilation of CA. In the study by Xu et al. (37), the high MDA level in the liver tissue of the CA-treated groups was reduced, and lipid peroxidation was minimized in the other groups. One possible explanation for the low level of MDA in the groups where EA and CA were administered together is that CA may act as a metal ion chelator, function as a strong scavenger of peroxyl radicals, and have a significant effect on lipid peroxidation (14).

In this study, we compared the treatments we applied with other groups, using PC levels, as well as MDA and NOx levels. Free radicals not only affect compounds such as lipids and nucleic acids through oxidative reactions, but they also react with important compounds such as proteins, causing various biological problems. One kind of oxidative protein alteration that is considered irreversible is protein carbonyl modification. They contain products of lipid peroxidation that disappear in a matter of minutes. Since protein oxidation happens very early during oxidative stress and is not caused by a

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

particular oxidant, we employed PC levels as a marker of protein oxidation in this work (38). In this study, the untreated groups showed a significant increase in PC levels after 7 days. This indicates that protein carbonyls remain in the bloodstream for a longer period than other oxidative stress markers. Without treatment, oxidative stress increases over time and protein dysfunction worsens. In a study conducted by Balabanlı and Balaban (39), where endotoxaemia was induced in rats, PC levels were found to be high in the endotoxin-treated group, which supports our finding. Our study revealed significant differences of protein carbonyl levels, depending on timing rather than application methods. A significant decrease was determined in the 7-day treatment group compared to both the untreated 7-day group and the topical 3-day group, regardless of the application method used. The significant decrease in PC levels in the tissue with EA and CA, is thought to be due to the protective impact of these two active substances on proteins from carboxylation. They also play an effective role in antioxidant metabolism in longer applications, both topical and oral. Although no significant difference was observed between the 7-day treatment groups, the strongest antioxidant effect was observed in the 7-day oral gavage treatment. Xiang et al. (16) found that oral administration of CA reduced protein carbonyls and showed antioxidant effects in LPS-induced liver damage. Karimi et al. (40) demonstrated that EA administration at 30 mg/kg orally significantly decreased elevated MDA, NOx, and protein carbonyl levels in toxin-induced hepatotoxicity, reversing oxidative damage. Moreover, the outcomes show that the inhibitory impact changes according to concentration. Therefore, further research should be conducted on the method, and duration of use of the CA and EA combination.

Antioxidant defence systems are crucial for protecting cells and tissues from damage caused by free radicals generated by reactive oxygen and nitrogen. GSH, an antioxidant synthesised from glutamate, cysteine and glycine in the liver, plays a vital role in this protection (29). In this study, GSH levels were significantly higher in all therapy groups compared to the control and untreated groups, indicating an increase in antioxidant capacity. Nisari (41) investigated the protective effect on antioxidant enzymes in the liver tissue of diabetic rats, and found a significant decrease in GSH activity. The study found that GSH production increased in liver tissue as a result of both oral and topical application of the two substances due to its antioxidant capacity against oxidative stress. The most significant increase in GSH was observed in the 7-day oral treatment group compared to the 3-day topical and 3-day oral treatment groups. This suggests that the two substances may be more effective in terms of bioavailability when administered orally, over a longer duration. The results of Shendge et al. (42) support our findings regarding the favourable effects of EA on oxidative stress in hepatotoxicity caused by iron overload. In their in vivo study, after determining the in vitro antioxidant capacity of EA, they found that ROS levels decreased, and SOD, CAT, GST, and GSH increased in the groups treated orally with EA, in liver tissue samples. The results of MDA and PC in EA-treated groups in this study are also consistent with our results previously discussed. Similarly, Das et al. (43) found results similar to ours regarding CA treatment. They showed that CA treatment (10 and 20 mg/kg) increased lipid peroxidation and protein carbonylation in hepatic tissue to levels close to normal. It also increased GSH and other endogenous antioxidant enzymes.

Another parameter used in the study was AA, an acronym for an important substance with non-enzymatic antioxidant properties similar to GSH. The statistically significant increase in AA levels in liver tissue in all treated groups, indicates an increase in antioxidant capacity. Devipriya et al. (12) conducted a study that yielded results similar to ours. They administered three different concentrations of EA intragastrically to evaluate its effects against alcohol-induced damage. The study found that AA in plasma increased along with other antioxidants, and oxidative stress was reduced by a decrease in liver marker enzymes. It is believed that CA may have an antioxidant effect, particularly by scavenging lipid peroxyl radicals, as reported in previous studies (14). The significant increase in GSH levels in all treated groups, administered via both topical and oral gavage applications, compared to the untreated groups, indicates an increase in antioxidant capacity. Previous studies have also reported a positive and significant correlation between AA supplementation and GSH levels (44). When evaluating the treated groups separately, no significant correlation was found among the topically treated groups. However, in the orally treated groups, the 7-day orally gavaged group showed a significant increase in AA compared to the 3-day orally gavaged group. This suggests that the two antioxidants may be more effective in terms of bioavailability when administered orally over a longer period of time. The results indicate a significant decrease in the 3-day oral group compared to the topically treated groups and the control group, suggesting that AA can effectively eliminate oxidative stress. Additionally, AA is used in all stages of wound healing, including apoptosis and phagocytosis of neutrophils, synthesis, and secretion of collagen. Therefore, it is possible that the level of AA was lower on the 3rd day of injury with oral application compared to topical application. The impact of EA and CA on AA in liver tissue may be more closely linked to the method of administration when examining our findings.

AA is essential for tissue formation and collagen synthesis. It converts proline, a non-essential amino acid found in collagen, into hydroxyproline (45). Collagen is a crucial matrix component that plays a significant role in cell proliferation and migration during the normal wound healing process. The number of myofibroblasts increases during the fibrosis period when collagen synthesis, which is necessary for extracellular matrix (ECM) formation, occurs. Various cellular subgroups and mechanisms in the liver, kidney, lung, heart, and skin contribute to extracellular matrix formation during fibrogenesis. The liver is a significant source of ECM production, with numerous cell types, including hepatic stellate cells, portal myofibroblasts, resident fibroblasts, and bone marrow-derived myofibroblast precursors. We investigated the effect of EA + CA applications on collagen levels in the liver because hepatic stellate cells and portal myofibroblasts, which perform collagen synthesis, originate from the liver (46). Previous studies have investigated the connection between epidermal adhesion and collagen as well as the migration of fibroblasts in the skin. Duckworth et al. (47) investigated the effect of EA on collagen and elastin production by administering retinoic acid to human dermal fibroblasts for varying periods. They found a significant increase in production and concluded that EA can improve fine wrinkles by enhancing elastin and collagen production. Using CA together with other chemicals, Darawsha et al. (48) investigated the protective impact of polyphenols, estradiol, and carotenoids on cutaneous fibroblasts under oxidative stress.

Gazi Med J 2025;36(2):152-161

Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

The compounds were pre-incubated in dermal cells, resulting in a decrease in the ROS level generated by H_2O_2, inhibition of cell death, reversal of the increase in MMP-1 secretion, and reversal of the decrease in pro-collagen levels caused by oxidative stress. In this study, we observed a significant increase in collagen levels in the treatment groups compared to the untreated groups, which is consistent with the findings of Duckworth et al. (47) and Darawsha et al. (48). The activation of the Nrf2 transcription pathway, which increases the production of antioxidant enzymes that lower ROS, is responsible for the increase in collagen in the EA + CA treated groups (48).

The study found a significant decrease in AA levels in the 3-day topical group, which showed the least increase in collagen levels. This suggests that AA, which is necessary for collagen synthesis, is used to eliminate oxidative stress, resulting in a low increase in collagen levels (45). Abdelkader et al. (28) conducted a study on VPA-induced liver toxicity. The treatment groups showed a significant decrease in the content of hydroxyproline, one of the collagen components, following the oral gavage administration of EA. In this study, we found that collagen levels in the liver tissue of the control group were higher than those of the wound-treated groups, which may be due to hyperglycaemic conditions. This suggests that EA and CA helped to eliminate hyperglycaemic conditions and maintain normal cell conditions. Numerous studies have investigated the effect of EA on collagen levels in various contexts, including hypertrophic scars, liver tissue affected by schistosoma, and myocardial infarction. The findings indicate that EA inhibits the proliferation and migration of fibroblasts by inhibiting the expression of collagen I, collagen III, MMP-2, and MMP-9, and ECM deposition. As a result, collagen fibre deposition is significantly reduced (49). Zhang et al. (50) conducted a study on the effect of CA on liver fibrosis. The study found that administering CA, intragastrically to rats, which were induced with bile duct ligation resulted in a reduction of α-smooth muscle actin and collagen 1 expression in the liver.

When considering the two different application methods of EA and CA in total, particularly in 7-day oral gavage and 7-day topical application, it can be inferred that EA and CA applications reduce lipid peroxidation and protein modification, increase antioxidant capacity, and achieve oxidative balance. This is supported by the decrease in MDA, NOx, and PC, as well as the increase in GSH, AA, and collagen. EA and CA may have a synergistic effect when used together, reducing inflammation and influencing cell behaviour under normoglycaemic conditions. The study suggests that EA and CA have a positive effect on liver tissue by reducing oxidative stress and inflammation, which is important for overall metabolic control. These findings contribute positively to the existing literature. EA and CA work together to reduce oxidative stress and inflammation by acting through the same pathway. The study shows that EA and CA increased antioxidant activity by upregulating Nrf2 expression in liver tissue. The Nrf2/Keap1 system regulates the expression of most endogenous antioxidants. Therefore, it can be concluded that EA and CA enhance antioxidant capacity and reduce oxidative stress by activating the Nrf2 pathway.

Study Limitations

The remarkable limitation of our study is the absence of data specific to enzymatic antioxidants and molecular signaling pathways.

CONCLUSION

The positive effect of two antioxidant substances, (EA and CA) on oxidative events in liver tissue was revealed, in this study, using a diabetic wound model. Thus, the positive effects of a mixture with potential use in diabetic wounds were revealed.

Ethics

Ethics Committee Approval: The Gazi University Laboratory Animal Committee Ethics Committee granted permission for the investigations (approval number: G.U.ET-20.012, date: 14.02.2022).

Informed Consent: : Informed consent was obtained from all participants included in the study.

Footnotes

Authorship Contributions

Concept: A.B., Ş.C.C., Design: A.B., Ş.C.C., Supervision: Ş.C.C., Resources: Ş.C.C., Data Collection or Processing: A.B., E.N.G., Ş.C.C., Analysis or Interpretation: A.B., E.N.G., Ş.C.C., Literature Search: A.B., E.N.G., Ş.C.C., Writing: K.K., Ş.C.C., Critical Review: K.K., Ş.C.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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Berktaş et al. Ellagic Acid, Carnosic Acid and Liver Oxidative Stress in Diabetic Rats

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Prognostic Factor and Survival Rate Among Breast Cancer Patients' Post-Surgical Treatment

Memedeki Kanser Hastalarının Cerrahi Tedavi Sonrası Prognostik Faktörler ve Sağkalım Oranı

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ABSTRACT

Objective: The prognosis of breast cancer patients is affected by various types of factors, such as the present stage of illness during the initial diagnosis. The goal of this study is to evaluate the biological factors that can be assessed before breast cancer surgery to predict the outcome of breast cancer surgery for patients who have already undergone the procedure.

Methods: STATA was utilised for reviewing and analysing the data obtained from the retrospective review of the breast cancer records, which focused on post-surgical treatment patient outcomes. Patients who underwent breast cancer surgery were analysed using the "Cox proportional hazards regression model" to evaluate the factors that predict survival rates. The data analysis includes 482 of breast cancer patients after surgical procedures.

Results: A total of 482 patients with breast cancer had surgical procedures from 2016 to 2019. In terms of survival rate, prognostic factors were associated with a poor prognosis for higher-grade tumours, advanced-stage breast cancers, and invasive lobular carcinoma tumour types.

Conclusion: Several clinical and pathological factors influence the overall prognosis and treatment choices. Therefore, it is crucial to adopt the right screening programme to diagnose breast cancer at an early stage. Healthcare practitioners must be aware of various therapeutic methods in the management of cancer to enhance the percentage of survival breast cancer patients

Keywords: Prognostic factor, survival rate, breast cancer, post-surgical

ÖZ

Amaç: Meme kanseri hastalarının prognozu, ilk tanı sırasında hastalığın mevcut evresi gibi çeşitli faktörlerden etkilenmektedir. Bu çalışmanın amacı, meme kanseri cerrahisi öncesinde değerlendirilebilecek biyolojik faktörleri değerlendirerek, meme kanseri cerrahisi geçirmiş hastaların prognozunu tahmin etmektir.

Yöntemler: Cerrahi tedavi sonrası hasta sonuçlarına odaklanan meme kanseri kayıtlarının retrospektif incelemesinden elde edilen verilerin gözden geçirilmesi ve analizi için STATA kullanılmıştır. Meme kanseri ameliyatı geçiren hastalar, sağkalım oranlarını öngören faktörleri değerlendirmek için "Cox orantılı tehlikeler regresyon modeli" kullanılarak analiz edilmiştir. Veri analizi, cerrahi işlem sonrası 482 meme kanseri hastasını kapsamaktadır.

Bulgular: 2016-2019 yılları arasında meme kanseri olan 482 hastaya cerrahi prosedür uygulanmıştır. Sağkalım oranı açısından, prognostik faktörler yüksek dereceli tümörler, ileri evre meme kanserleri ve invaziv lobüler karsinom tümör tipleri için kötü prognoz ile ilişkilendirilmiştir.

Sonuç: Çeşitli klinik ve patolojik faktörler genel prognozu ve tedavi seçeneklerini etkilemektedir. Bu nedenle, meme kanserinin erken evrede teşhis edilmesi için doğru tarama programının benimsenmesi büyük önem taşımaktadır. Sağlık hizmeti uygulayıcıları, meme kanseri hastalarının hayatta kalma yüzdesini artırmak için kanser yönetiminde çeşitli terapötik yöntemlerin farkında olmalıdır.

Anahtar Sözcükler: Prognostik faktör, sağ kalım oranı, meme kanseri, ameliyat sonrası

Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer

INTRODUCTION

Globally, breast cancer is the primary cause of mortality among cancers affecting women, with 685 thousand reported deaths among women in 2020 (1). The number of breast cancer cases worldwide increased to around 6,232,000 between 2008 and 2012, with this accounting for 15.8 percent of cancer-related fatalities, as reported by (2). The Global Cancer Burden Study, a recent comprehensive investigation, unveiled a substantial increase in the incidence of breast cancer, as an estimated 2.3 million individuals are anticipated by 2020 (3). Approximately 16.5 percent of all officially reported cancer cases in 2016 were female breast cancer cases and 4,621 cases were registered with the Malaysia National Cancer Registry. A Malaysian woman has a 50 percent lifetime potential of becoming a breast cancer patient (4). The incidence of cancer in Malaysia is projected to rise because of the growing life expectancy, improved socio-economic position, and evolving lifestyles. Malaysia recorded a total of 8,418 new cases and 3,503 fatalities in 2020 (5).

Furthermore, based on the GLOBOCAN cancer tomorrow prediction tool, there may be a global increase of over 46 percent in incident cases by 2040 (6). Incredible progress has already been made in the past twenty years in refining subatomic cluster formation and enhancing the prognosis for malignant breast growth to improve survival (7). Additional endeavours to combat worldwide breast cancer encompass prevention, timely identification, diagnosis and treatment, rehabilitation, and palliative care (8). Prevention and early detection, such as promoting breast cancer awareness, is paramount in reducing mortality. Our facility in Kota Kinabalu, Sabah, has a long-standing surgical programme for treating breast cancer, and we have maintained a population-based cancer registry. However, there is no publication on evaluating prognostic factors for breast cancer post-surgery. Therefore, this study seeks to evaluate the prognostic biological factors affecting the outcomes in breast cancer patients with post-surgical procedures.

MATERIALS AND METHODS

This study was conducted at the Breast Pink Ribbon Clinic in a tertiary hospital located in the west coast of Kota Kinabalu, Land Below the Wind. It was carried out as a retrospective cohort analysis. This study involved women who were diagnosed with breast cancer and had undergone breast surgery procedures, including wide local excision, mastectomy with axillary clearance, mastectomy, mastectomy with reconstruction, and mastectomy conserving, between 1 January 2016 and 31 December 2019, who were the only participants. The tumour types were invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and others. There was no sampling strategy applied because all patients who satisfied the inclusion criteria and had breast cancer surgery during the study period were included. We excluded participants who failed to adhere to the treatment, had missing medical records, or declined surgical intervention. The data collection form was created to document the demographic features of patients the prognostic variables influencing the survival rate, and the prognosis of breast cancer patients.

The sample size needed for this study has been determined to apply a multivariable model through the "Cox proportional hazard regression model". The objective was to evaluate the prognostic influences affecting the survival rate of patients with breast cancer who had undergone surgery procedures. To determine these sample size, the "rule of thumb" approach, requires a minimum of ten occurrences per predictor parameter (9). The total sample size was determined to be 482. A Microsoft Excel spreadsheet was used to document the data initially, and then STATA/SE12.0 was applied to conduct additional statistical analysis.

The "Cox proportional hazard regression analysis" was applied to evaluate the prognostic variables that influence the rates of post-operative survival among breast cancer patients. The main aim was to construct a mathematical representation of the time until an event occurs and its connection to a group of explanatory factors while accounting for instances where the event did not occur within the observed period. The multivariable Cox proportional hazard regression analysis considered additional variables that were identified as potential factors influencing the dependent variable. The automated variable selection approach was used to perform the best subset selection and determine the components that would create the most concise model, given the available data. The results of the assumption tests for the "Cox proportional hazard regression model" were displayed simultaneously with each model. The probability values were two-tailed. A p-value below 0.05 was considered statistically significant. The studies were authorised by the Malaysian Research Ethics Committee and certified by the National Malaysian Research Registry Medical Review and Ethical Committee from the National Institute of Health, Ministry of Health [approval number: NMRR-20-27-52650 (IIR), date: 12.02.2020].

RESULT

Table 1 presents a concise overview of the participants' key demographic characteristics and clinical classifications, highlighting their outcomes and associated p-values for understanding the findings. Our study engaged a diverse group of 482 participants, yielding a mean age of 52.1 years (standard deviation =11.7). The age distribution provided valuable insights, revealing that over half of the participants, specifically 53.1%, were aged over 50 years, indicative of a mature cohort. Meanwhile, 29.7% fell within the 41 to 50-year range, while 15.4% were aged between 30 and 40 years. Only 1.9% of the participants were younger than 30 years. The participants exhibited a range of body mass index (BMI) values, with an average BMI of 26.4 kg/m² and a standard deviation of 5.2. The categorization of participants by BMI highlighted distinct weight profiles: 2.7% were classified as underweight (BMI <18.5 kg/m²), a substantial 41.1% maintained a normal weight (BMI 18.5-24.9 kg/m²), while 34.2% were identified as overweight (BMI 25-29.9 kg/m²). Lastly, 21.9% of participants fell into the obese category (BMI ≥30 kg/m²).

Tumour size was predominantly in the 2 to 5 cm range (55.8%), while 27.6% of participants had tumours larger than 5 cm and 16.6% had tumours smaller than 2 cm. Tumor staging revealed that 39.6% of cases were at stage 2, 28.8% at stage 4, 23.9% at stage 3, and 7.7% at stage 1. Tumor grading indicated that 19.9% of tumors were grade 1, 47.5% were grade 2, and 32.6% were grade 3. Regarding tumour type, 95.6% of cases were IDC, 1.8% were ILC, and 2.5% were categorized as other types.

Hormonal receptor statuses showed that 72.6% of participants were estrogen receptor-positive, while 27.4% were negative. Progesterone

Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer

Table 1. Demographic features & clinical states of the participants

Variable	Total: 482 n (%)	Mean (SD)	Outcome		p
			Alive n (%)	Dead n (%)	
Age (Years)		52.1 (11.7)	52.1 (11.7)	51.8 (13.5)	0.910
<30	9 (1.9)				
30-40	74 (15.4)				
41-50	143 (29.7)				
>50	256 (53.1)				
BMI (kg/m^2)		26.4 (5.2)	26.4 (5.1)	27.6 (6.4)	0.317
<18.5	13 (2.7)				
18.5-24.9	198 (41.1)				
25-29.9	165 (34.2)				
≥30	106 (21.9)				
Size of tumour (cm)					
<2	80 (16.6)		78 (16.8)	2 (11.1)	0.005
>2-5	269 (55.8)		264 (56.9)	5 (27.8)	
>5	133 (27.6)		122 (26.3)	11 (61.1)	
Stage					
1	37 (37.7)		37 (7.9)	0 (0.0)	0.001
2	191 (39.6)		190 (40.9)	1 (5.6)	
3	115 (23.9)		110 (23.7)	5 (27.8)	
4	139 (28.8)		127 (27.4)	12 (66.7)	
Grade of tumour					
1	96 (19.9)		96 (20.7)	0 (0.0)	0.013
2	229 (47.5)		222 (47.8)	7 (38.9)	
3	157 (32.6)		146 (31.5)	11 (61.1)	
Tumor type					
IDC	461 (95.6)		446 (96.1)	15 (83.3)	0.038
ILC	9 (1.8)		8 (1.7)	1 (5.6)	
Others	12 (2.5)		10 (2.2)	2 (11.1)	
Status of progesterone receptor					
Positive	289 (60)		227 (48.9)	9 (50)	0.929
Negative	193 (40)				
Status of estrogen receptor					
Positive	350 (72.6)		338 (72.8)	12 (66.7)	0.564
Negative	132 (27.4)				
Status of human epidermal growth factor receptor					
Positive	236 (49)		227 (48.9)	9 (50)	0.929
Negative	246 (51)				
Lymph node affected					
1 to 3	99 (46.1)		99 (47.8)	0 (0.0)	0.008
4 to 9	81 (37.7)		76 (36.7)	5 (62.5)	
≥10	35 (16.3)		32 (15.5)	3 (37.5)	
Lymph node ratio					
<0.20	340 (70.5)		330 (71.1)	10 (55.6)	0.137
0.20-0.65	93 (19.3)		89 (19.2)	4 (22.2)	
>0.65	49 (10.2)		45 (9.7)	4 (22.2)	

BMI: Body mass index, SD: Standard deviation

Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer

receptor positivity was observed in 60% of participants, with 40% being negative. Human epidermal growth factor receptor 2 (HER2) receptor status was positive in 49% of participants and negative in 51%. Lymph node involvement was categorized into three groups: 46.1% of participants had 1 to 3 lymph nodes affected, 37.7% had 4 to 9 lymph nodes affected, and 16.3% had 10 or more lymph nodes affected. The lymph node ratio was <0.20 in 70.5% of cases, 0.20-0.65 in 19.3%, and >0.65 in 10.2%.

A comprehensive Cox proportional hazards regression analysis was conducted to rigorously evaluate how clinical and pathological factors influence patient outcomes (Table 2). In the simple regression analysis, tumour size greater than 5 cm (HR =3.57, p=0.009), stage 4 disease (HR =4.50, p=0.007), and grade 3 tumours (HR =3.20, p=0.016) were significantly associated with increased hazard. The cumulative hazard estimates for cancer stages as a prognostic factor for survival are shown in Figure 1. The cumulative hazard estimates for cancer tumour grade as a prognostic factor for survival are illustrated in Figure 2. Also, the cumulative hazard estimates for tumour type as a prognostic factor for survival are presented in Figure 3.

Table 2. Prognostic factor of breast cancer survival after surgical procedure by "Cox proportional hazard model" (n=482)

Variable	Regression Coefficient (b)	Simple Cox regression hazard ratio (95% CI)	Z statistic	p	Regression coefficient (b)	Multiple Cox regression adjusted hazard ratio (95% CI)	Z statistic	p
Age	0.01	1.00 (0.96,1.04)	0.04	0.966				
BMI	0.20	1.04 (0.97,1.12)	0.29	0.285				
Tumour Size (cm)								
≤5	0	1						
>5	1.27	3.57 (1.38,9.22)	2.63	0.009				
Stage								
1 to 3	0	1			0	1		
4	1.50	4.50 (1.69,12.00)	2.70	0.007	1.42	4.13 (1.54,11.11)	2.82	0.005
Grade of tumour								
1 to 2	0	1			0	1		
3	1.16	3.20 (1.24,8.27)	2.41	0.016	1.4	4.07 (1.50,11.01)	2.76	0.006
Tumour type								
IDC	0	1			0	1		
ILC and Others	1.38	3.97 (1.15,13.7)	2.18	0.029	1.86	6.43 (1.75,23.69)	2.8	0.005
Progesterone receptor								
Negative	0	1	-1.40	0.162				
Positive	-0.66	0.52 (0.20,1.31)						
Estrogen receptor status								
Negative	0	1						
Positive	-0.33	0.72 (0.27,1.92)	-0.66	0.51				
HER2 receptor								
Negative	0	1						
Positive	0.02	1.02 (0.41,2.57)	0.04	0.966				
Lymph node affected								
0	0	1						
≥1	0.01	1.01 (0.40,2.56)	0.02	0.980				
Lymph node ratio								
<0.20	0	1						
0.20-0.65	0.44	1.56 (0.49,4.97)	0.75					
>0.65	1.01	2.73 (0.86,8.71)	1.70	0.089				

BMI: Body mass index, SD: Standard deviation, HER2: Human epidermal growth factor receptor 2, IDC: Ductal carcinoma, ILC: Invasive lobular carcinoma, CI: Confidence interval

Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer
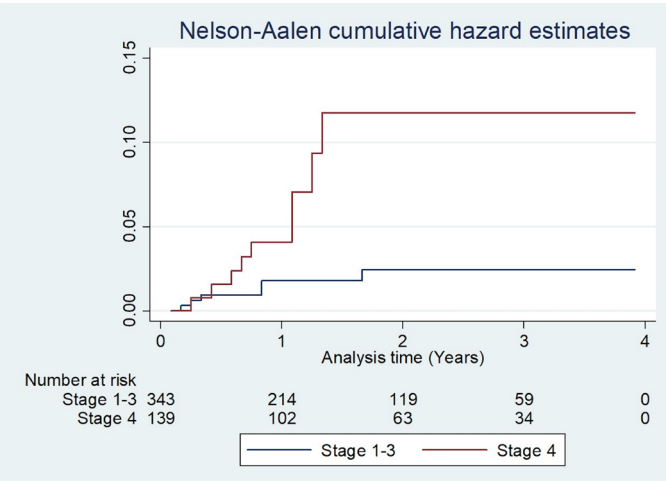
Figure 1. Cumulative hazard estimates for cancer stages as a prognostic factor for survival.
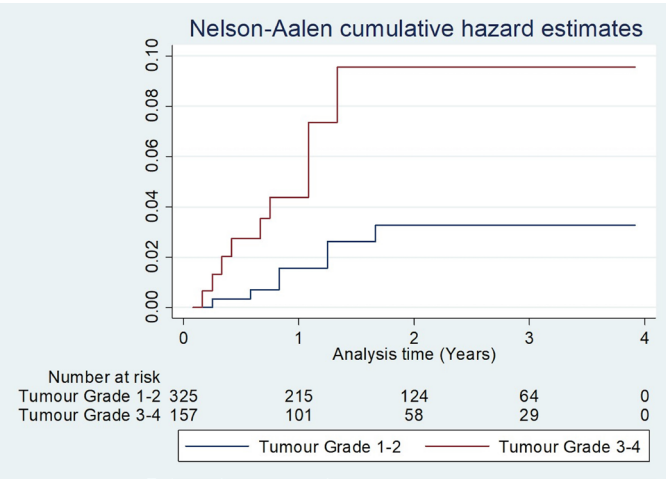
Figure 2. Cumulative hazard estimates for cancer tumour grade as a prognostic factor for survival.
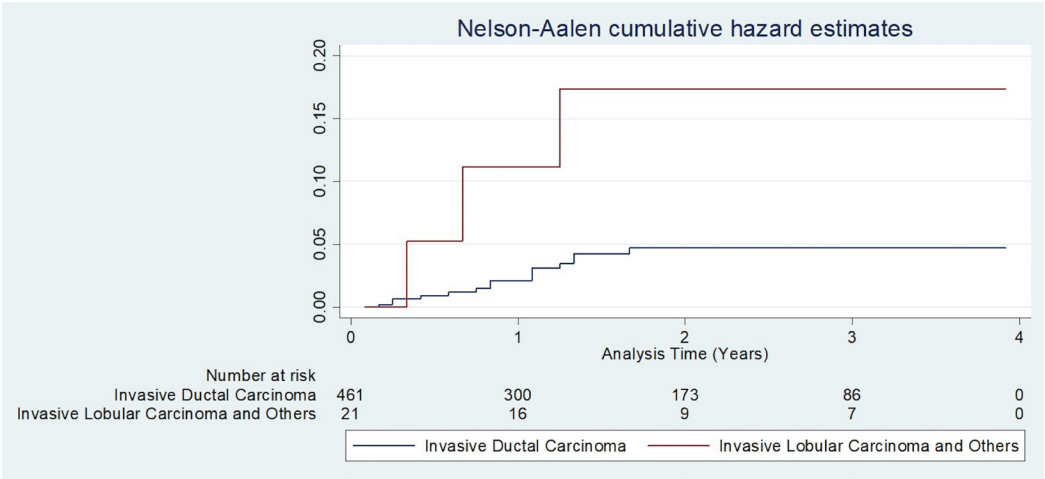
Figure 3. Cumulative hazard estimates for type of tumour as a prognostic factor for survival.

Additionally, ILC and other tumour types showed a higher risk than IDC (HR =3.97, p=0.029). Hormone receptor status, HER2 positivity, and lymph node involvement were not significantly associated with hazard ratios. In the multiple regression analysis, stage 4 disease (Adjusted HR =4.13, p=0.005), grade 3 tumours (Adjusted HR =4.07, p=0.006), and ILC (Adjusted HR =6.43, p=0.005) remained significant predictors of poor outcomes.

DISCUSSION

The results from this study indicate that tumour size, stage, grade, and histological type significantly influence survival outcomes. These findings are consistent with previous studies demonstrating the prognostic importance of tumour characteristics in cancer progression. Tumour size greater than 5 cm was associated with a significantly increased hazard ratio, which is consistent with the study by (7), who reported that histologic grade remains a significant prognostic factor for overall survival, independent of tumour size. This finding emphasizes the necessity of early detection and intervention to improve patient prognosis. Advanced disease stage, especially stage 4, remained among the strongest predictors of poor outcomes. This is consistent with previous studies (8), which found that metastatic disease at the time of diagnosis drastically reduces survival rates. This emphasizes how crucial prompt staging and vigorous treatment are for advanced cases in clinical practice.

In our study, grade 3 tumours had considerably higher hazard ratios. Previous research, such as that conducted by (9), has designated the Nottingham histological grade as a key predictive indicator for breast cancer, vital for clinical decision-making. This emphasizes the importance of personalized treatment approaches, particularly for individuals with high-grade tumours who may benefit from intensive therapy. Histological tumour type was another key prognostic factor, with ILC and other variants exhibiting a significantly increased hazard compared to IDC. This aligns with previous studies indicating that ILC often presents with unique biological behaviour and a higher likelihood of late recurrences compared to IDC (10,11). These findings suggest that histological subtyping should be carefully considered when planning long-term patient management and follow-up strategies. Hormone receptor status, HER2 positivity,

Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer

and lymph node involvement did not correlate significantly with hazard ratios. While prior research has demonstrated that hormone receptor-positive tumours generally have a more favourable prognosis (9,12), our study revealed no statistically significant difference, underscoring the robustness of our findings. This may be due to sample size limitations or differences in treatment modalities, suggesting the need for further investigation.

Our study reinforces the importance of tumour staging, grading, and histological classification in determining prognosis and guiding treatment decisions. Clinicians should prioritize early detection, as tumour size and stage are critical determinants of survival, which is in line with current guidelines from the American Joint Committee on Cancer (13). Staging at diagnosis significantly affects treatment options, with advanced-stage cancers requiring more aggressive and multimodal treatment strategies, including chemotherapy, targeted therapy, and radiotherapy (14). The observed differences in outcomes based on tumour grade and histology highlight the need for personalized treatment approaches. For instance, high-grade tumours and lobular carcinoma subtypes have been shown to exhibit aggressive behaviour and increased recurrence risk, necessitating more intensive follow-up and adjuvant therapy (15,16). Advances in molecular profiling and genomic testing now allow for a more individualized approach, helping to identify patients who may benefit from novel targeted therapies or immunotherapies (17).

Furthermore, the lack of significant findings for hormone receptor status and lymph node involvement suggests that additional prognostic markers may be required to refine risk stratification. Current guidelines emphasize the integration of genomic and molecular profiling, such as the Oncotype DX and MammaPrint assays, into clinical practice to improve patient selection for chemotherapy and endocrine therapy (18). The shift toward precision medicine could reduce overtreatment while ensuring high-risk patients receive appropriate interventions. Future research should focus on further integrating AI-driven risk assessment tools and biomarker-based therapies into routine oncology care (19).

Study Limitations

Preliminary research conducted in Kota Kinabalu; Sabah aimed to determine prognostic factors influencing postoperative survival rates in breast cancer patients. However, the study had limitations, including a brief time frame and incomplete data regarding breast cancer occurrence and death rates in Sabah. Therefore, certain prognostic factors and risk factors for breast cancer, such as clinical presentation, socio-economic status, and educational level, were not recorded or analysed due to missing or incorrectly written histopathology data. Future research should employ prospective, multicentre studies incorporating genetic profiling and molecular subtyping to provide a more holistic understanding of prognostic determinants. Additionally, addressing barriers to early detection, such as healthcare access disparities, remains a critical area for intervention.

CONCLUSION

Advanced breast cancer, higher tumour grade, and ILC tumour type are all associated with a poorer survival prognosis in patients. Identifying the risk factors for breast cancer recurrence is crucial

as it can guide the selection of initial treatment strategy, assist in subsequent monitoring, and provide accurate information to patients. Our analysis of the results showed a higher proportion of younger patients were developing breast cancer. Thorough assessment of breast-conserving surgery is recommended for young patients with positive axillary lymph nodes. These women should receive rigorous post-surgical therapy and comprehensive follow-up. Prompt and accurate identification, along with timely access to appropriate therapy, is essential for reducing breast cancer mortality rates. Increasing awareness about breast cancer, instilling confidence in its manageability, and improving access to comprehensive primary healthcare, including skilled breast physical examinations, can potentially improve survival rates.

Ethics

Ethics Committee Approval: The studies were authorised by the Malaysian Research Ethics Committee and certified by the National Malaysian Research Registry Medical Review and Ethical Committee from the National Institute of Health, Ministry of Health [approval number: NMRR-20-27-52650 (IIR), date: 12.02.2020].

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.H., N.A.S.N.L., Concept: F.H., R.K., Design: F.H., N.A.S.N.L., Supervision: F.H., N.A.S.N.L., S.Z.S., J.E.L., Resources: R.K., N.A.S.N.L., Material: S.Z.S., Data Collection or Processing: R.K., J.E.L., Analysis or Interpretation: R.K., J.E.L., Literature Search: R.K., D.L., D.C.C., Writing: R.K., D.C.C., D.L., Critical Review: R.K., D.C.C., D.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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Gazi Med J 2025;36(2):162-168

Kumilau et al. Prognostic Factors & Survival in Post-Surgical Breast Cancer

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Evaluation of Postoperative Pain in Patients Undergoing Erector Spinae Plane Block in Breast Surgeries

Meme Cerrahilerinde Erektör Spina Plan Blok Yapılan Hastalarda Postoperatif Dönemde Ağrının Değerlendirilmesi

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ABSTRACT

Objective: Postoperative pain remains a significant issue in mastectomy patients, and in recent years, regional block techniques have been frequently used in treatment. In this study, we evaluated the analgesic efficacy of erector spinae plane block (ESPB) in patients undergoing breast surgery.

Methods: Our study was conducted retrospectively by reviewing the data from medical records of 94 adult female patients with ASA I-II-III who underwent breast surgery. Patients were divided into two groups: the control group (Group 1) and the ESPB group (Group 2). Both groups received postoperative intravenous patient-controlled analgesia (IV-PCA) tramadol for 24 hours. The primary objective was to assess pain intensity and postoperative opioid requirement using the visual analogue scale (VAS) score. Additionally, postoperative hemodynamic data, adverse effects, demand for bolus tramadol from PCA, number of bolus doses received, total tramadol dose given, need for additional analgesia, and patient satisfaction were evaluated.

Results: No difference was found in postoperative hemodynamic data. VAS scores at postoperative 1st, 2nd, and 4th hours were significantly higher in the control group than the ESP group (p=0.002, p<0.0001, p=0.005, respectively). Postoperative nausea and vomiting were observed in 9.1% of patients in Group 1, whereas none were observed in Group 2, and this difference was significant in Group 1 (X^2=4.747, p=0.029). Additional analgesic requirement at 12 hours was observed in 20.5% of patients in Group 1, while 2% in Group 2, and the difference was significant (X^2=8.385, p=0.004). There was no significant difference between the groups in terms of PCA data and patient satisfaction.

ÖZ

Amaç: Mastektomi hastalarında postoperatif ağrı halen önemli bir sorun olmaya devam etmekte ve bu konuda son yıllarda rejyonel blok teknikleri tedavide sıklıkla kullanılmaktadır. Biz bu çalışmada meme cerrahisi geçiren hastalarda uygulanan erektör spina plan bloğun (ESPB) analjezik etkinliğini değerlendirdik.

Yöntemler: Çalışmamız meme cerrahisi geçiren ASA I-II–III 94 yetişkin kadın hastanın verileri dosya kayıtlarından retrospektif olarak taranarak gerçekleştirildi. Hastalar kontrol grubu (Grup 1) ve ESPB (Grup 2) olarak iki gruba ayrıldı. Her iki gruba da 24 saat boyunca postoperatif intravenöz hasta kontrollü analjezi (İV-HKA) tramadol uygulandı. Birincil hedef olarak görsel analog ölçek (VAS) skoru kullanılarak ağrı şiddeti ve postoperatif opioid ihtiyacının değerlendirilmesi amaçlandı. Ayrıca hastaların postoperatif hemodinamik verileri, oluşan yan etkiler, tramadol HKA'dan sağlanan bolus talebi (demand), kaç kez bolus doz tramadol aldığı (bolus) ve total verilen tramadol dozu, ek analjezik ihtiyacı ve hasta memnuniyetleri değerlendirildi.

Bulgular: Postoperatif hemodinamik veriler arasında farklılık tespit edilemedi. Postoperatif 1., 2., ve 4. saat ölçüm VAS değerleri kontrol grubunda ESP grubuna göre anlamlı olarak yüksek bulundu (p=0.002, p<0.0001, p=0.005, sırasıyla). Postoperatif 1. saat bulantı kusma Grup 1'de hastaların %9.1'inde görülürken Grup 2'de hiçbir hastada görülmedi ve Grup 1'de anlamlı olarak fazla tespit edildi (X^2=4.747, p=0.029). Ek analjezi ihtiyacı 12. saatte Grup 1'de hastaların %20.5'inde, Grup 2'de ise %2'sinde görülüp anlamlı farklılık tespit edildi (X^2=8.385, p=0.004). Her iki grupta HKA verileri ve hasta memnuniyetleri açısından anlamlı bir farklılık tespit edilmedi.

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Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

ABSTRACT

Conclusion: Although ESP block reduced VAS scores in the early postoperative hours, we did not detect any effect on total tramadol consumption.

Keywords: Erector spinae plane block, mastectomy, postoperative pain, patient-controlled analgesia, opioid consumption, tramadol

ÖZ

Sonuç: ESP blok postoperatif erken saatlerdeki VAS değerlerini düşürmesine karşın toplam tramadol tüketimi üzerine herhangi bir etkisini tespit edemedik.

Anahtar Sözcükler: Erektör spina plan bloğu, mastektomi, postoperatif ağrı, hasta kontrollü analjezi, opioid tüketimi, tramadol

INTRODUCTION

Breast cancer, being one of the most commonly diagnosed cancers, is primarily and most effectively treated with surgical resection (1). However, many patients experience severe postoperative acute pain following surgery. Studies indicate that 60% of women complain of severe acute pain (2). Consequently, both the acute pain itself and the side effects associated with opioids commonly used in treatment can distress patients. Moreover, untreated acute pain can become chronic and significantly reduce patients' quality of life (3). Therefore, a variety of medications and regional techniques can be used in postoperative pain management. However, an optimal method for postoperative analgesia in breast surgery has not yet been defined. In recent years, new regional anesthesia techniques such as fascial plane blocks have begun to be preferred by clinicians for this purpose. Erector spinae plane block (ESPB), successfullyapplied and described by Forero et al. (4) for thoracic neuropathic pain, has been successfully applied in breast surgery by Bonvicini et al. (5). ESPB has become a popular block in recent times due to its ease of procedure and very low complication rates when performed under ultrasound guidance. Its contribution to analgesia management has been observed in many surgical areas when applied at different levels, and its use in daily practice is becoming more widespread. However, debates about its effectiveness continue (6). In this study, we aimed to investigate the effect of preoperative ESPB at the T4 level on postoperative opioid requirement and outcomes in patients undergoing radical mastectomy, with or without axillary lymph node dissection surgery.

MATERIALS AND METHODS

This study was conducted retrospectively between February 1, 2022, and August 1, 2022, at the Department of Anesthesiology and Reanimation, Gazi University Faculty of Medicine after obtaining ethics committee approval (approval number: 2022-03/1690, date: 27.01.2022). Female patients aged 18 and over with ASA (American Society of Anesthesiologists) I-II-III undergoing radical mastectomy or radical mastectomy with axillary lymph node dissection were identified from medical records and detailed postoperative analgesia forms routinely filled out in our clinic.

Patients undergoing mastectomy (radical mastectomy and radical mastectomy with axillary lymph node dissection) were brought to the operating table, and their vital parameters were monitored. Standard general anesthesia was administered using endotracheal intubation (induction with propofol, remifentanil, and rocuronium, followed by maintenance with sevoflurane and remifentanil). After endotracheal intubation, patients scheduled for ESPB were placed in the lateral decubitus position. The T4 spinous process was localized with palpation assistance. After ensuring appropriate sterilization conditions, ultrasound (LOGIQ e, GE Healthcare, USA) was used

to visualize the transverse process in the lateral aspect, 2-2.5 cm from the midline. Once the transverse process was visualized, the procedure began using a 22-gauge, 50 mm needle (SonoPlex®) (Figure 1). After confirming the location between the transverse process and erector spinae muscle using hydrodissection, 20 mL of 0.25% bupivacaine (Marcaine vial, Eczacıbaşı, Türkiye) was injected into this area to perform the unilateral ESPB procedure.

In our clinic, all patients undergoing mastectomy surgery routinely receive intravenous (IV) tramadol patient-controlled analgesia (PCA) for postoperative analgesia. Using data obtained from medical records, patients who received only general anesthesia were designated as the control group (Group 1), while those who received general anesthesia along with ESPB formed Group 2.

Demographic data of the patients (age, body weight, ASA classification) were recorded from the medical records. Operation duration (minutes), postoperative visual analogue scale (VAS) pain scores at rest at 0 (control), 1, 2, 4, 6, 12, and 24 hours, systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP) values (mmHg), and heart rates (HR) (beats/min) were recorded from the postoperative analgesia record forms. Postoperative side effects, demand for bolus tramadol from PCA, number of bolus doses received, total tramadol dose given (mg), need for additional analgesics (20 mg tenoxicam), and patient satisfaction were assessed and recorded using a four-point scale (1: lowest, 4: highest).

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 software. Statistical analysis data were presented as mean ± standard deviation, standard error, (minimum-maximum), and n (%). The distribution of measurable parameters was determined as normal or abnormal

Figure 1. The ultrasound image shows the ESPB procedure performed at the T4 vertebral level using an in-plane linear probe in our clinic.

ESPB: Efficacy of erector spinae plane block

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

by applying the Kolmogorov-Smirnov test. Group comparisons for variables such as age, body weight, operation duration, PCA total and bolus, and patient satisfaction were assessed using the Student's t-test. ASA, PCA demand and bolus requirements, side effects, number of patients receiving additional analgesics, and patient satisfaction were evaluated using the chi-square or Fisher's exact chi-square tests. Repeated measures analysis of variance was used to assess variables such as HR, SBP, DBP, MAP, and VAS scores. Post-hoc Scheffe test was applied for between-group comparisons in case of significance. In repeated measures variance analysis, the within-group control values of HR, SBP, DBP, MAP, and VAS data, where the time factor was significant, were compared using the Post-hoc Bonferroni test. A test result was considered significant if $p<0.05$.

RESULTS

A total of 94 patients with ASA I-II-III classification were included in this study. There were no statistically significant differences in demographic characteristics between the patient groups included in our study (Table 1). When comparing the operation durations between the groups, it was observed that there was no significant difference, and the mean operation durations were similar in both groups (Table 2). The average values of HR data at different measurement times are shown in Table 3. When comparing the HR averages in terms of changes over time, no significant difference was found between the groups. However, when investigating intra-group differences over time, relative to the control value, it was observed that in Group 1, the mean HR values at 1 and 2 hours were statistically different from the control HR average ($p<0.0001$, $p=0.004$, respectively). In Group 2, the mean HR values were statistically different from the control HR average at the respective measurement times ($p<0.0001$, $p<0.0001$, $p=0.001$, $p=0.001$, $p=0.002$, $p=0.001$, respectively) (Table 3).

The average values of systolic blood pressure (SBP) data at different measurement times are shown in Table 4. When comparing the SBP averages between the groups in terms of changes over time,

no significant difference was found between the groups. However, when investigating intra-group differences over time relative to the control value, it was observed that in both groups, the mean SBP values were statistically different from the control SBP average at all measurement times ($p<0.0001$, all). The average values of diastolic blood pressure (DBP) data at different measurement times are shown in Table 5. When comparing the DBP averages between the groups in terms of changes over time, no significant difference was found between the groups. However, when investigating intra-group differences over time relative to the control value, it was observed that in both groups, the mean DBP values were statistically different from the control DBP average at all measurement times (Group 1 control-2nd hour, $p=0.002$; Group 1 control-4th hour, $p=0.001$; Group 2 control-1st hour, $p=0.004$, others $p<0.0001$).

The average values of MAP data at different measurement times are presented in Table 6. When comparing the MAP averages between the groups in terms of changes over time, no significant difference was observed between the groups. However, when investigating intra-group differences over time relative to the control value, it was noted that in both groups, the mean MAP values were statistically different from the control MAP average at all measurement times except the 1st hour, ($p<0.0001$, all). The average values of VAS data at different measurement times are presented in Table 7. When comparing the VAS averages between the groups in terms of changes over time, VAS values at the 1st, 2nd, and 4th-hour measurements were found to be significantly higher in Group 1 compared to Group 2 ($p=0.002$, $p<0.0001$, $p=0.005$, respectively). When investigating intra-group differences over time relative to the control value, it was observed that in Group 1, the mean VAS values at the 4th, 6th, 12th, and 24th hour were statistically different from the control VAS average ($p=0.003$, $p<0.0001$, $p<0.0001$, $p<0.0001$, respectively), while in Group 2, the mean VAS values were statistically different from the control VAS average at all measurement times except the 1st hour ($p=0.004$, $p<0.0001$, $p<0.0001$, $p<0.0001$, $p<0.0001$, respectively), (Table 7).

Table 1. Demographic characteristics of the cases in the groups [Mean ± SD (Min.-Max.), n (%)]

	Group 1 (n=44)	Group 2 (n=50)	p
Age (year)	56.55±12.96 (34-88)	54.60±12.59 (32-79)	0.463
Body weight (kg)	74.18±14.44 (50-123)	68.98±12.61 (46-102)	0.068
ASA (I/II/III)	3(6.8)/30(68.2)/11(25)	4(8)/32(64)/14(28)	$X^2=0.185$ p=0.912

SD: Standard deviation, Min.: Minimum, Max.: Maximum, ASA: American Society of Anesthesiologists

Table 2. Operation time [Mean ± SD (Min.-Max.)]

	Group 1 (n=44)	Group 2 (n=50)	p
Operation time (Min.)	134.30±38.04 (60-230)	136.10±38.35 (60-240)	0.820

SD: Standard deviation, Min.: Minimum, Max.: Maximum

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

Table 3. Distribution of heart rates (beats/min.) in groups [Mean ± SD (Min.-Max.)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control	84.75±17.86 (54-133)	84.14±11.58 (53-112)	0.843
1st hour	74.70±11.15+ (60-103)	77.80±11.64+ (58-98)	0.193
2nd hour	76.68±9.51+ (56-102)	77.02±10.67+ (58-100)	0.872
4th hour	78.27±10.93 (55-116)	77.34±10.25+ (56-96)	0.671
6th hour	78.98±9.85 (58-110)	77.52±11.70+ (57-100)	0.519
12th hour	80.64±7.76 (60-95)	77.88±10.14+ (56-98)	0.146
24th hour	80.27±7.36 (62-101)	77.80±9.11+ (58-97)	0.155

+: p<0.05 (compared to within-group control).
SD: Standard deviation, Min.: Minimum, Max.: Maximum

Table 4. Distribution of systolic arterial blood pressures (mmHg) between groups [Mean ± SD (Min.-Max.)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control	136.86±24.75 (97–205)	135.46±21.68 (100-180)	0.770
1st hour	119.80±15.74+ (80-160)	120.02±14.85+ (90-150)	0.943
2nd hour	117.20±14.17+ (100-160)	116.36±14.00+ (90-150)	0.772
4th hour	115.27±12.05+ (90-140)	113.82±12.50+ (90-140)	0.569
6th hour	113.80±10.37+ (100-130)	112.58±11.77+ (90-140)	0.599
12th hour	111.93±10.41+ (95-135)	113.34±10.45+ (90-140)	0.515
24th hour	112.27±10.76+ (90-140)	114.24±9.34+ (100-130)	0.345

+: p<0.05 (compared to within-group control).
SD: Standard deviation, Min.: Minimum, Max.: Maximum

Table 5. Distribution of diastolic arterial blood pressures (mmHg) in groups [Mean ± SD (Min.-Max.)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control	80.09±14.64 (57-139)	81.86±13.54 (51-113)	0.544
1st hour	71.89±9.82+ (40-100)	73.90±10.73+ (60-100)	0.348
2nd hour	71.55±9.82+ (60-100)	71.26±10.32+ (40-90)	0.891
4th hour	70.68±8.26+ (60-85)	70.36±8.67+ (60-90)	0.855
6th hour	67.39±7.21+ (60-80)	68.70±8.48+ (60-82)	0.424
12th hour	70.25±7.17+ (60-80)	71.02±7.05+ (60-90)	0.601
24th hour	69.70±7.76+ (50-82)	71.06±7.98+ (60-82)	0.407

+: p<0.05 (compared to within-group control),
SD: Standard deviation, Min.: Minimum, Max.: Maximum

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

Side effects determined in the postoperative period are given in Table 8. The only side effects detected were postoperative nausea and vomiting (PONV). While PONV was seen in 9.1% of the patients in Group 1, it was not seen in any patient in Group 2 and was detected significantly more in Group 1 (X^2=4.747, p=0.029). It was found to be similar at other measurement times. PCA data are presented in Table 9. PCA total tramadol consumption via PCA was found to be similar in the demand and bolus groups. The need for postoperative additional analgesia (tenoxicam 20 mg) is presented in Table 10. At the 12th hour, the requirement for additional analgesia was observed in 20.5% of patients in Group 1 and 2% of patients in Group 2. The number of patients requiring additional analgesia at the 12th hour was significantly higher in Group 1 (X^2=8.385, p=0.004). Similar observations were made at other measurement times. Patient satisfaction was found to be similar between the groups (Table 11).

Table 6. Distribution of mean arterial blood pressures (mmHg) between groups [Mean ± SD (Min.-Max.)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control	99.01±16.93 (70–161)	99.73±15.20 (71-135)	0.830
1st hour	87.86±11.06 (53-120)	89.27±10.12 (72-110)	0.537
2nd hour	86.77±10.66+ (73-120)	86.29±10.11+ (63-106)	0.826
4th hour	85.55±8.29+ (70-101)	84.85±9.28+ (72-106)	0.703
6th hour	82.86±6.93+ (73-96)	83.33±8.84+ (70-100)	0.777
12th hour	84.14±6.80+ (71-96)	85.13±6.94+ (70-106)	0.491
24th hour	83.89±8.00+ (63-100)	85.45±7.55+ (73-96)	0.334

+: p<0.05 (compared to within-group control),
SD: Standard deviation, Min.: Minimum, Max.: Maximum

Table 7. Distribution of visual analogue scale values across groups [Mean ± SH (Min.-Max.)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control (Postoperative first VAS score)	4.68±0.53 (0-10)	3.84±0.42 (0-9)	0.215
1st hour	5.45±0.45 (0-10)	3.54±0.38* (0-10)	0.002
2nd hour	4.34±0.37 (0-9)	2.46±0.29*,+ (0-8)	<0.0001
4th hour	3.14±0.30+ (0-8)	2.00±0.23*,+ (0-6)	0.005
6th hour	1.93±0.28+ (0-7)	1.36±0.20+ (0-5)	0.093
12th hour	1.45±0.29+ (0-9)	0.88±0.13+ (0-4)	0.077
24th hour	1.39±0.25+ (0-6)	0.92±0.20+ (0-9)	0.144

*: p<0.05 (compared with group 1),
+: p<0.05 (compared to within-group control).
SD: Standard deviation, Min.: Minimum, Max.: Maximum, VAS: Visual Analogue Scale

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

Table 8. Postoperative nausea and vomiting (PONV) [n (%)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Control (Postoperative first VAS score)	1 (2.3)	-	X^2=1.530 p=0.468
1st hour	4 (9.1)	-*	X^2=4.747 p=0.029
2nd hour	2 (4.5)	-	X^2=2.322 p=0.128
4th hour	2 (4.5)	-	X^2=2.322 p=0.128
6th hour	2 (4.5)	1 (2)	X^2=0.496 p=0.481
12th hour	2 (4.5)	-	X^2=2.322 p=0.128
24th hour	-	-	-

*: $p<0.05$ (compared with group 1)
VAS: Visual Analogue Scale

Table 9. Patient-controlled analgesia (PCA) data [Mean ± SD (Min.-Max.), n (%)]

	Group 1 (n=44)	Group 2 (n=50)	p
PCA tramadol total (mg)	188.82±17.45 (29.6-500)	222.23±13.71 (118-498.5)	0.131
PCA demand	14.38±6.06 (1-91)	9.65±2.70 (1-89)	0.447
PCA bolus	5.18±1.13 (1-21)	6.87±2.20 (1-88)	0.516
PCA demand (yes/no)	34(77.3)/10(22.7)	43(86)/7(14)	X^2=1.203 p=0.273
PCA bolus (yes/no)	34(77.3)/10(22.7)	40(80)/10(20)	X^2=0.104 p=0.747

PCA: Patient-controlled analgesia

Table 10. Distribution of additional analgesia to groups [n (%)]

Time	Group 1 (n=44)	Group 2 (n=50)	p
Time	15 (34.1)	13 (26)	X^2=0.733 p=0.392
Control	10 (22.7)	6 (12)	X^2=1.907 p=0.167
1st hour	10 (22.7)	12 (24)	X^2=0.021 p=0.884
2nd hour	7 (15.9)	4 (8)	X^2=1.417 p=0.234
4th hour	7 (15.9)	9 (18)	X^2=0.072 p=0.788
6th hour	9 (20.5)	1 (2)*	X^2=8.385 p=0.004
12th hour	6 (13.6)	2 (4)	X^2=2.791 p=0.095

*: $p<0.05$ (compared with group 1)

DISCUSSSION

Postoperative pain remains a significant issue following breast cancer surgery, leading to chronic persistent pain in approximately half of the patients (7). Therefore, investigating effective techniques to reduce postoperative pain is crucial. In this study, we aimed to investigate the postoperative analgesic effects of ESPB in radical mastectomy, and radical mastectomy with axillary lymph node dissection. The results of our study revealed that ESPB did not affect postoperative hemodynamic parameters. However, VAS scores at 1st, 2nd, and 4th hours were significantly higher in the control group compared to the ESPB group. Despite there being no significant postoperative side effects or complications observed in either group, the incidence of PONV at the 1st hour was significantly higher in the control group compared to the ESPB group. Additionally, there was a significantly higher need for rescue analgesia at the 1st hour in the control group compared to the ESPB group, despite similar total tramadol consumption, demand, and bolus requests from the PCA system between the groups. Furthermore, patient satisfaction did not differ between the two groups.

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

Table 11. Patient satisfaction with anesthesia [Mean ± SD (Min.-Max.), n(%)]

	Group 1 (n=44)	Group 2 (n=50)	p
Patient satisfaction	3.23±0.67 (1-4)	3.10±0.73 (2-4)	0.385
Patient satisfaction (1/2/3/4)	1(2.3)/3(6.8)/25(56.8)/15(34.1)	0(0)/11(22)/23(46)/16(32)	X^2=5.326 p=0.149

SD: Standard deviation, Min.: Minimum, Max.: Maximum

When examining the effects of ESPB on hemodynamic parameters, we found no significant difference between the groups. These findings are consistent with previous studies in the literature (8,9). In our study, no patient in the ESPB group experienced any complications related to the block technique. Besides PONV in the perioperative period, no other side effects or complications were encountered. The observed incidence of PONV at the 1st hour was 9.1% in the control group, while no patients in the ESPB group experienced PONV. This difference was statistically significant ($X2$=4.747, p=0.029). However, no significant differences were noted at other measurement times. In a meta-analysis conducted by Hussain et al. (6), evaluating the analgesic benefits of adding ESPB to parenteral analgesia in twelve studies (699 patients), complications related to the block were assessed in eight studies, with no complications reported in any patients, while opioid-related side effects were reported in eleven studies. Compared to patients who received parenteral opioids, lower rates of nausea and vomiting were reported in patients who received ESPB. Similarly, another meta-analysis reported lower rates of PONV in patients who received ESPB (10). These findings are consistent with the low incidence of PONV observed in the ESPB group at the first hour in our study. He W et al. (11) suggested that ESPB slightly reduced the incidence of PONV (10% vs. 30%) in patients undergoing mastectomy with axillary lymph node dissection or radical mastectomy, attributing this to the potential reduction in intraoperative opioid doses due to ESPB use. We speculate that the higher incidence of nausea and vomiting observed at the 1st hour in the control group may be related to the higher doses of opioids used intraoperatively in this group, despite effective analgesia in the ESPB group during the intraoperative period.

In our study when comparing VAS mean scores between groups over time, we found that VAS scores at 1st, 2nd, and 4th hours were significantly higher in the Control group compared to the ESPB group (p=0.002, p<0.0001, p=0.005, respectively). Zhang et al. (10) conducted a meta-analysis of 11 randomized controlled trials involving 679 patients, in which they compared the ESPB group with the general anesthesia group. They found that the ESPB group had lower pain scores at four time points (1, 6, 12, and 24 hours after surgery) compared to the general anesthesia group. This is consistent with our study findings, where VAS scores at 1st, 2nd, and 4th hours were lower in the ESPB group. We believe that the lack of differences at other time points in our study may be attributed to the duration of block, and the tramadol and additional analgesics administered via IV PCA in both groups.

Studies have shown that ESPB reduces postoperative morphine consumption in breast surgery (9,10). Gürkan et al. (12) found that ESPB significantly reduced total morphine consumption from IV PCA at postoperative 1 hour, 6 hours, 12 hours, and 24 hours, compared

to the control group, in breast surgery. However, Hussain et al. (6) reported in their meta-analysis that adding ESPB to parenteral analgesia provided statistically significant, but clinically insignificant, short-term benefits following breast cancer surgery. They suggested that routine use of ESPB is not supported, and its benefits and risks should be evaluated on a case-by-case basis. Although the study by Gürkan et al. (12) was methodologically similar to ours, we did not find a statistically significant difference in total tramadol doses administered via IV PCA over 24 hours, compared to the control group (188.82±17.45 vs. 222.23±13.71 mg, respectively). The rich and complex innervation of breast tissue, the different neuronal structure of the axillary region, and breast tails, and unclear mechanisms related to the spread of ESPB may contribute to different results in studies involving this block (13-17). In our study, we applied ESPB at the T4 level, which is commonly preferred in breast surgery. However, it has been shown that a block applied at the T3 level is more effective in relieving pain in the chest wall and in the axillary region (11).

Although studies have shown that ESPB reduces 24-hour morphine consumption and the need for additional postoperative analgesics (9,10), we did not observe any differences in other time intervals except for the lower requirement for additional analgesia (tenoxicam) in the ESP group at 12 hours (20.5% vs. 2%). We believe that the reason for this could be the sufficiency of tramadol analgesia administered via PCA in both groups. The apparent difference at this time interval may be due to the inadequacy of analgesia during movement, patients in both groups experienced mobilization during this time, despite having sufficient rest. Although ESPB has been reported to increase patient satisfaction in breast surgery (18), Hussain et al. (6) stated in their meta-analysis evaluating the analgesic benefits of adding ESPB to parenteral analgesia following breast cancer surgery that, compared to parenteral opioids, ESPB did not increase patient satisfaction. Similarly, in our study, we did not observe any difference patient satisfaction between the two groups.

Study Limitations

We believe that the most significant limitation of our study is its retrospective design. Additionally, a limitation is that due to the lack of a prospective design, we could not determine the time of the first analgesic requirement.

CONCLUSION

The application of ESPB in mastectomy patients significantly reduced VAS scores in the postoperative first 4 hours without affecting hemodynamic parameters. However, we could not detect any effect on the total tramadol consumption over 24 hours. Although

Gazi Med J 2025;36(2):169-176

Kara et al. Erector Spinal Plane Block in Breast Surgeries

ESPB appears promising in controlling postoperative analgesia and reducing opioid-related side effects and complications, we believe that further randomized controlled trials are needed in this field.

Ethics

Ethics Committee Approval: Gazi University Faculty of Medicine after obtaining ethics committee approval (approval number: 2022-03/1690, date: 27.01.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: G.K., M.A., R.K., M.Ar., Design: G.K., M.A., R.K., N.C.E., Supervision: M.A., M.Ar., Data Collection or Processing: G.K., M.A., R.K., N.C.E., Analysis or Interpretation: G.K., R.K., N.C.E., Literature Search: G.K., R.K., N.C.E., Writing: G.K., R.K., R.K., Critical Review: M.A., M.Ar.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Rutin Protects Pancreatic Islets Against Methylglyoxal-Induced Oxidative Stress and Elevates Insulin Secretion

Rutin, Metilglioksal Kaynaklı Oksidatif Strese Karşı Pankreatik Adacıkları Korur ve İnsülin Salgılanmasını Artırır

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ABSTRACT

Objective: Hyperglycemia is the main characteristic of diabetes, which leads to complications, including oxidative stress (OS). Pancreatic β-cells are susceptible to damage against OS, which results in a disruption in insulin secretion. The current study focused on the antioxidant features of rutin (Rtn) flavonoid to prevent methylglyoxal (MG-)induced oxidative damage in pancreatic islets isolated from mice.

Methods: After isolating islets from twenty-four male mice, we conducted two experimental parts, (1) with exposure to MG- and (2) without exposure to MG. Experiments were carried out in both culture media with 5.6- and 16.7-mM glucose concentrations. Islets were transferred to the culture medium and exposed to different substances. In the end, insulin secretion, antioxidant enzyme activities, and malondialdehyde (MDA) concentration were investigated by ELISA.

Results: The reduced levels of insulin in MG-exposed islets (p=0.01, p<0.001 in 5.6- and 16.7-mM glucose concentration, respectively) were reversed by Rtn treatment. MG- increased MDA levels in 5.6- and 16.7-mM glucose concentrations (p<0.001 for 5.6 mM and p=0.005 for 16.7 mM. Also, we observed a remarkable decrease in the activities of catalase, superoxide dismutase, and glutathione peroxidase due to 300 μM MG- exposure in islets, in 5.6- and 16.7-mM glucose concentrations. Rtn at doses of 1 and 2 μM significantly reduced MDA levels. Moreover, Rtn had beneficial effects on antioxidant activities.

ÖZ

Amaç: Hiperglisemi, diyabetin temel özelliğidir ve oksidatif stres (OS) dahil olmak üzere çeşitli komplikasyonlara yol açar. Pankreatik β-hücreleri OS'ye karşı hassastır ve bu durum insülin salgılanmasında bozulmaya neden olur. Bu çalışma, rutin (Rtn) flavonoidinin antioksidan özelliklerine odaklanarak, metilglioksal (MG) kaynaklı oksidatif hasara karşı farelerden izole edilen pankreatik adacıkları koruma potansiyelini incelemektedir.

Yöntemler: Yirmi dört erkek fareden adacıklar izole edildikten sonra, iki deneysel bölüm gerçekleştirildi: (1) MG'ye maruz bırakılan grup ve 2. MG'ye maruz bırakılmayan grup. Deneyler, 5.6 mM ve 16.7 mM glukoz konsantrasyonlarına sahip kültür ortamlarında yapıldı. Adacıklar kültür ortamına aktarıldı ve farklı maddelere maruz bırakıldı. Son olarak, insülin salgılanması, antioksidan enzim aktiviteleri ve malondialdehit (MDA) konsantrasyonu ELISA yöntemiyle incelendi.

Bulgular: MG'ye maruz bırakılan adacıklarda azalan insülin seviyeleri (5.6 mM glukoz konsantrasyonu için p=0.01, 16.7 mM glukoz konsantrasyonu için p<0.001), Rtn tedavisi ile tersine çevrildi. MG, 5.6 mM ve 16.7 mM glukoz konsantrasyonlarında MDA seviyelerini artırdı (5.6 mM için p<0.001 ve 16.7 mM için p=0.005). Ayrıca, 300 μM MG'ye maruz bırakılan adacıklarda katalaz, süperoksit dismutaz ve glutatyon peroksidaz aktivitelerinde belirgin bir azalma gözlemlendi. Rtn'nin 1 ve 2

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ABSTRACT

Conclusion: Rtn significantly protected pancreatic islets by reducing lipid peroxidation and enhancing antioxidant activity. The decreased insulin levels in MG-exposed islets were effectively restored in the Rtn-treated groups.

Keywords: Flavonoids, hyperglycemia, insulin, methylglyoxal, oxidative stress, rutin

ÖZ

2 µM dozları, MDA seviyelerini önemli ölçüde azalttı. Bunun yanı sıra, Rtn antioksidan aktiviteler üzerinde olumlu etkiler gösterdi.

Sonuç: Rtn, lipid peroksidasyonunu azaltarak ve antioksidan aktiviteyi artırarak pankreatik adacıkları önemli ölçüde korudu. MG'ye maruz kalan adacıklarda azalan insülin seviyeleri, Rtn ile tedavi edilen gruplarda etkili bir şekilde geri kazanıldı.

Anahtar Sözcükler: Flavonoidler, hiperglisemi, insülin, metilglioksal, oksidatif stres, rutin

INTRODUCTION

Diabetes is a progressive metabolic disease that affects the lives of millions of people and is characterized by high blood glucose. One of the key factors contributing to the development of diabetes is the inability of pancreatic beta-cells to produce sufficient insulin, which leads to hyperglycemia [1,2]. Hyperglycemia causes increased glycolysis reactions, overproduction of reactive oxygen species (ROS), and ultimately impairs cell function and survival [3]. Hyperglycemia increases oxidative stress (OS) and contributes to insulin dysfunction and insufficient insulin secretion in diabetes. Moreover, a decrease in antioxidant mechanisms occurs in diabetes, which can further increase OS [4].

On the other hand, hyperglycemia can cause methylglyoxal (MG) accumulation, which is associated with various diabetes complications. MG, the active carbonyl metabolite, is derived from glucose, fatty acids, and protein metabolism and is responsible for producing free radicals in tissues [5]. The MG has a diverse range of effects on pancreatic β-cells, including diminished insulin secretion, induction of insulin resistance, initiation of free radical-induced apoptosis, and decreased cell mass [6].

OS plays an important role in the pathophysiology of diabetes. More precisely, OS causes inflammatory responses and β-cell dysfunction, decreasing insulin sensitivity in peripheral tissues [7]. The antioxidant content of pancreatic islets is low, so it can be inferred that these cells are more sensitive to OS [8]. Furthermore, low levels of antioxidants in the blood are a risk factor for chronic diseases such as diabetes, confirming that antioxidants are important in treating and preventing diabetes [9].

Glibenclamide (Glb), a member of sulfonylurea, stimulates pancreatic beta cells to release insulin and provides effective treatment for patients with diabetes [10]. This drug is widely used in patients with early diabetes. Although drugs such as sulfonylureas and metformin are widely used to manage diabetes, protecting pancreatic β-cells appears to help prevent or delay disease onset. Therefore, studying the effects of antioxidants, especially natural compounds, on pancreatic islets is one of the goals of diabetes treatment [11]. Many studies have reported that flavonoid compounds in plants show various therapeutic properties in the prevention and development of numerous diseases [12-14]. Flavonoids are suggested to act as an anti-diabetic agent by regulating blood glucose levels, promoting muscle glucose uptake, increasing insulin secretion, inhibiting glucose synthesis, reducing insulin resistance, and decreasing apoptosis of pancreatic beta-cells [15,16]. Rutin (Rtn) (quercetin-3-rhamnosyl-glucoside) is a common flavonoid found in plants such as tea, apples, onions, and many others [17]. This bioactive substance has many benefits including strong antioxidant effects, anti-inflammatory effects, and free radical scavenging [16,18]. Potentially anti-diabetic effects of Rtn are observed in both *in vitro* and *in vivo* research, and underlying mechanisms have been suggested, including hypoglycemic activity, insulin sensitivity improvement, and repair of damaged islet cells [19,20]. Until now, no study has evaluated the protective effects of Rtn on MG-exposure pancreatic islets. For this purpose, we designed this *in vitro* study to further evaluate these results, and investigate the impact of Rtn on antioxidant activity and insulin secretion of isolated pancreatic islets exposed to MG.

MATERIALS AND METHODS

Animals

Twenty-four Naval Medical Research Institute adult male mice (25-35 g) were purchased from the central animal house of Ahvaz Jundishapur University of Medical Sciences. They were maintained in a room at 22°C±2°C with a 12:12 h light/dark cycle. Animals had free access to standard laboratory food and water. This study is reported under the Research Center & Experimental Animal House-Ahvaz Jundishapur University of Medical Sciences Ethics Committees (approval number: IR.AJUMS.ABHC.REC.1401.035, date: 16.08.2022). This study is not applicable because it involves animal subjects.

Sample Size

In this research, the pancreatic tissue of 24 animals was analyzed using Minitab software with the values of $\alpha=0.05$ and $\beta=0.2$, assuming a 35% drop.

Drugs and Chemicals

Drugs used for this study, such as MG and Glb, were obtained from Sigma (St. Louis, MO, USA). Rtn was purchased from Solgar Company, USA. Ketamine 10% and xylazine 2% from Alfasan Co. (The Netherlands). Krebs-bicarbonate buffer (KBB) ingredients were all purchased from Merck (Germany).

Experimental design

Pancreas islets isolation

The isolation of islets was performed by the collagenase digestion method as described previously [21]. Briefly, after anesthetizing the subject, the pancreas tissues were removed and transferred to KBB, manually homogenized, and centrifuged for 5 min (100×g). Twelve milligrams of P-type collagenase per pancreas were added to remove the exocrine portion of the tissues, in combination with

KBB for the deposition process. The tube was then placed in an oscillating incubator at 37°C for 5-10 min. Cold KBB was poured into the conical tubes to stop collagenase degradation; the tubes were centrifuged for 5 min at 500 g. The pancreatic islets were separated manually using a stereo microscope and cultured in Hank's buffer.

Islets cultures

This study was carried out in two separate parts, including experiment 1, (samples exposed to 300 µM MG for 30 min in both normal and hyperglycemic conditions) and experiment 2, (without MG exposure, in both normal and hyperglycemic conditions). Ten isolated islets were used in all groups.

Experiment 1:

MG: Incubation of islets with MG +2 h incubation (6).

Glb + MG: Incubation of islets with MG + Glb to reach the concentration of 10 µM +2 h incubation.

Rtn0.5 + MG: Incubation of islets with MG + 0.5 µM of Rtn to reach the concentration of 0.5 µM + incubation for 2 h.

Rtn1+MG: Incubation of islets with MG + 1 µM of Rtn to reach the concentration of 1 µM + 2 h incubation.

Rtn2+MG: Incubation of islets with MG+ 2 µM of Rtn to reach the concentration of 2 µM +2 h incubation.

Experiment 2:

Glb: Islets received 10 µM of glibenclamide (as a reference drug) + incubation for 2 h and 30 min (21).

Rtn0.5: Islets received 0.5 µM of Rtn incubation for 2 h and 30 min (22).

Rtn1: Islets received 1 µM of Rtn+ incubation for 2 h and 30 min.

Rtn2: Islets received 2 µM of Rtn + incubation for 2 h and 30 min.

The control groups (Ctl) of the experiments included 10 isolated islets that were incubated in both normal and hyperglycemic conditions for the same time.

Biochemical Analysis

Insulin Assessment

The islets were transferred in a microtube in KBB (1 mL). At first, islets were incubated with MG for 30 min, Rtn and Glb were administered for 2 h at 37°C, and then centrifuged at 100 xg for 5 min. The supernatant was transferred at -70°C. The insulin concentration was determined using a colorimetric assay kit (Monobind Inc, USA) following the manufacturer's instructions.

Measurement of Malondialdehyde, Superoxide Dismutase, Catalase, and Glutathione Peroxidase Contents

Malondialdehyde (MDA) content, superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities were measured using a commercial kit (ZellBio GmbH, Germany) according to the manufacturer's instructions.

Statistical Analysis

At first, the data was normalized by the Shapiro-Wilk test (alpha=0.05). Statistical analyses were performed using GraphPad Prism 9 for Windows (GraphPad Software, San Diego, CA). One-way ANOVA was used to analyze the differences between groups, followed by the post hoc Tukey test. Levene's test was used for homogeneity of variances. The data were represented as mean ± SD, and $p < 0.05$ was considered significant.

Results

Effect of Rtn and Glb on insulin secretion in isolated pancreatic islets

As presented in Table 1, the insulin levels increased when Glb and Rtn2 were administered alone in normal and hyperglycemic conditions ($p < 0.05$). As shown in Table 2, MG diminished insulin secretion in normal glucose conditions (p=0.01). The levels of insulin in all treated groups, such as Glb + MG ($p < 0.01$), Rtn0.5 + MG

Table 1. Effect of Rtn and Glb on insulin secretion of isolated pancreatic islets without MG presence

	Control	Glb	Rtn0.5	Rtn1	Rtn2	p
Insulin secretion						
a	42.42±6.891	54.12±1.896*	44.5±2.184	46.74±2.165	49.43±1.49*	0.018
b	44.51±3.781	54.42±0.9768*	48.07±4.07	49.09±3.07	56.04±3.428*	0.008

*Significant difference with control, one symbol: $p < 0.05$.
Glb: Glibenclamide, Rtn0.05: Rutin 0.05 µM, Rtn1: Rutin 1 µM, Rtn2: Rutin 2 µM, a: normoglycemic condition, b: hyperglycemic condition

Table 2. Effect of Rtn and Glb on insulin secretion of isolated pancreatic islets in the presence of MG

	Control	MG	Glb + MG	Rtn0.5 + MG	Rtn1 + MG	Rtn2 + MG	p
Insulin secretion							
a	43.42±5.5	31.41±0.7*	46.63±2.3##	45.66±2.45##	45.34±5.32##	49.17±1.65###	<0.001
b	44.51±3.8	28.98±4.3***	37.07±0.8*#	38.62±1.4##	43.59±1.4###	44.50±2.5###$	<0.001

*Significant difference with control, # significant difference with MG group, $ significant difference with MG + Glb group; one symbol: $P < 0.05$, two symbol $P < 0.01$, three symbol $p < 0.001$.
MG: Methylglyoxal, Glb + MG: Glibenclamide + 300 µM methylglyoxal, Rtn0.05 + MG: Rutin 0.05 µM + 300 µM methylglyoxal, Rtn1 + MG: Rutin 1 µM + 300 µM methylglyoxal, Rtn2 + MG: Rutin 2 µM + 300 µM methylglyoxal, a: normoglycemic condition, b: hyperglycemic condition

(p<0.01), Rtn1 + MG (p<0.01), and Rtn2 + MG (p<0.001) improved. As observed in Table 2, in hyperglycemic conditions, insulin levels were decreased in the MG (p<0.001) and Glb + MG (p<0.05) groups, when compared to the Ctl. There were significant differences when the Glb + MG (p=0.03), Rtn0.5 + MG (p=0.009), Rtn1 + MG (p<0.001), and Rtn2 + MG (p<0.001) were compared to the MG group. Additionally, the insulin levels of Rtn2 + MG (p<0.05) increased effectively compared to those in the Glb + MG group.

Effect of Rtn and Glb in Islet's Lipid Peroxidation

As reported in Figure 1, MDA increased in the MG (p<0.001), Glb + MG (p<0.001), and Rtn0.5 + MG (p=0.004) compared to the Ctl. Applying 1 and 2 μM of Rtn effectively reduced lipid peroxidation (p=0.02; P=0.04, respectively). Additionally, 1 μM of Rtn demonstrated a superior effect compared to the Glb + MG group (p=0.05).

In hyperglycemic conditions, the MDA levels in the MG and MG + Glb groups were higher than the Ctl group (p=0.005 and p=0.006, respectively). Treatment with 2 μM of Rtn, reduced it (p=0.007). The difference between Rtn2 + MG and Glb + MG was significant (p=0.008) (Figure 1).

Effect of Rtn and Glb on Antioxidant Activity in Isolated Pancreatic Islets

In general, the lowest activity of SOD was observed in the MG group in both culture media. In the 5.6 mM glucose condition, MG reduced the SOD activity of islets compared to the Ctl (p=0.009). The treatment of islets exposed to MG with 0.5 (p=0.02), 1 (p<0.001), and 2 (p=0.004) μM of Rtn, remarkably improved SOD activity compared with the MG group (Figure 2). In the hyperglycemic condition, MG decreased the SOD activity (p=0.003). Treatment with 0.5, 1, and 2 μM of Rtn recovered the SOD activity compared to the MG group (p=0.04, p=0.01, p=0.01, respectively) (Figure 2).

As presented in Figure 3, the level of GPx in the MG group was lower than the Ctl (p=0.009). While Rtn at doses 1 (p=0.003) and 2 (p=0.002) μM restored the amounts of GPx compared to the MG, further studies are needed to confirm the long-term effects. In hyperglycemic conditions, the suppressed levels of GPx in the MG group reversed in the Rtn1 + MG and Rtn2 + MG groups (p=0.02 and p=0.002, respectively). Additionally, the levels of GPx in the Rtn2 + MG group were higher than those in the Glb + MG group (p=0.05) in hyperglycemic islets (Figure 3).

MG reduced the CAT activity of pancreatic islets in normal (p=0.009), and hyperglycemic conditions (p=0.02), compared to the Ctl (Figure 4). Treatment with 1 μM (p=0.003) and 2 μM (p=0.002) of Rtn,

Figure 1. Effects of rutin on MDA levels with (a,b) and without (c,d) MG. Data are represented as mean ± SD.

Compared with control; # compared with MG; $ compared with Gly + MG. One symbol: p<0.05, two symbol: p<0.01, three symbol: p<0.001

Figure 2. Effects of rutin on SOD activity with (a,b) and without (c,d) MG. Data are represented as mean ± SD.

Compared with control; # compared with MG. One symbol: p<0.05, two symbol: p<0.01, three symbol: p<0.001

augmented CAT activity compared to the MG group in islets under normal glucose conditions. Furthermore, the CAT activity was enhanced in the Rtn0.5 + MG ($p=0.005$), Rtn1 + MG ($p=0.003$), and Rtn2 + MG ($p=0.003$) groups compared to the MG group in hyperglycemic islets (Figure 4). Administration of Rtn at doses 1 µM ($p=0.008$) and 2 µM ($p=0.01$) improved the CAT activity in hyperglycemic non-MG-exposed islets (Figure 4).

DISCUSSION

MG, as an active component of glucose, has a detrimental effect on cellular function by stimulating ROS production and oxidative damage to pancreatic β-cells (12). Indeed, the reaction of MG and proteins results in advanced glycation end products that contributes to the induction of intracellular ROS and the development of OS (5). Additionally, during hyperglycemia, the normal signaling pathway called "glycolysis" in pancreatic β-cells is saturated, so excess glucose enters several sub-pathways associated with ROS production. Meanwhile, the antioxidant capacity renders pancreatic islets more sensitive to OS. Superoxide anion is one of the reactive metabolites of mitochondrial electron transport chain, and is converted to H_2O_2 by SOD and finally to H_2O and O_2 by CAT and Gpx enzymatic activity. OS is a pivotal factor in the onset and promotion of diabetes (7). An oxidative environment can lead to β-cell dysfunction and insulin resistance, which in turn can lead to diabetes (23). This study used mouse-derived primary islets to demonstrate the protective effect of Rtn on islet cells. Our results indicated that 300 mM MG damaged pancreatic islets. MG has been reported to cause cytotoxicity in pancreatic INS-1 cells by stimulating OS and mitochondrial dysfunction (24). Our results showed that MG (300 mM) increased MDA levels in pancreatic beta-cells under normal and hyperglycemic conditions. MDA is the end-product of polyunsaturated fatty acids and indicates lipid oxidation (25). Accumulating evidence confirms that MG causes OS and that impaired membrane integrity leads to lipid peroxidation, which is observed with the release of MDA from the membrane as a cytotoxic metabolite (26). It is also observed as a marker of insulin expression dysfunction and diabetes (27). Bioactive compounds in medicinal plants are now considered an alternative approach in the treatment of numerous diseases owing to their low side effects and healthy therapeutic efficacy (28). Rtn is a flavonoid compound found in many plants, and has various biomedical properties (29,30). The property of Rtn to scavenge free radicals was previously discovered (18). Free radicals are formed through various biological reactions. It has been reported that the concentration and position of hydroxyl groups determine the capacity to neutralize free radicals in phenolic compounds. Furthermore, *in vitro* studies showed that Rtn inhibited egg yolk lipid peroxidation in a dose-dependent manner (29). A study reported that oral administration of Rtn to rats with streptozotocin-induced diabetes has anti-
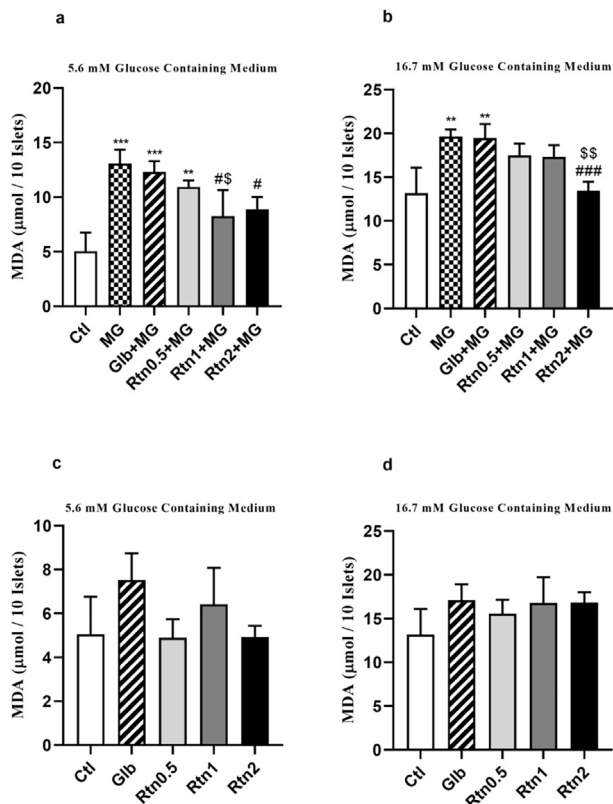

Figure 3. Effects of rutin on GPx concentration with (a,b) and without (c,d) MG. Data are represented as mean ± SD.

Compared with control; # compared with MG; $ compared with Gly + MG. One symbol: $p<0.05$, two symbol: $p<0.01$, three symbol: $p<0.001$
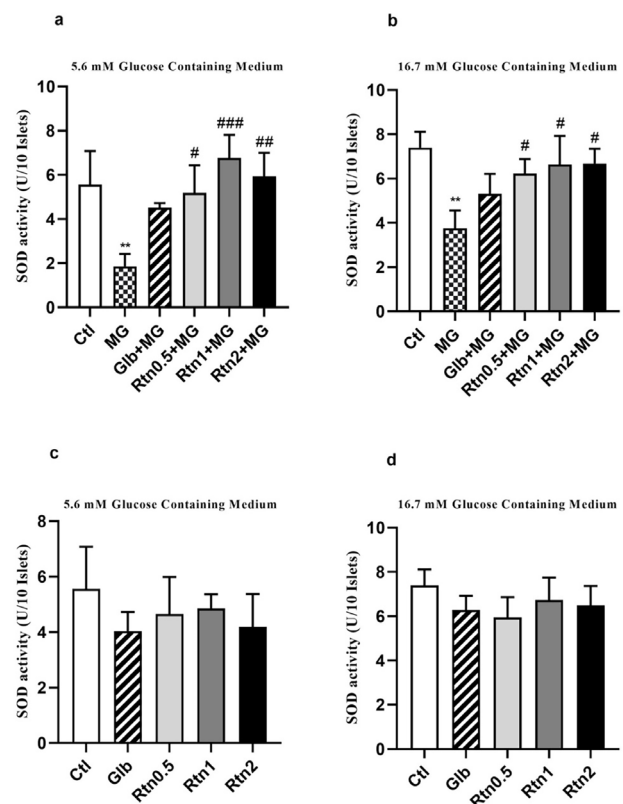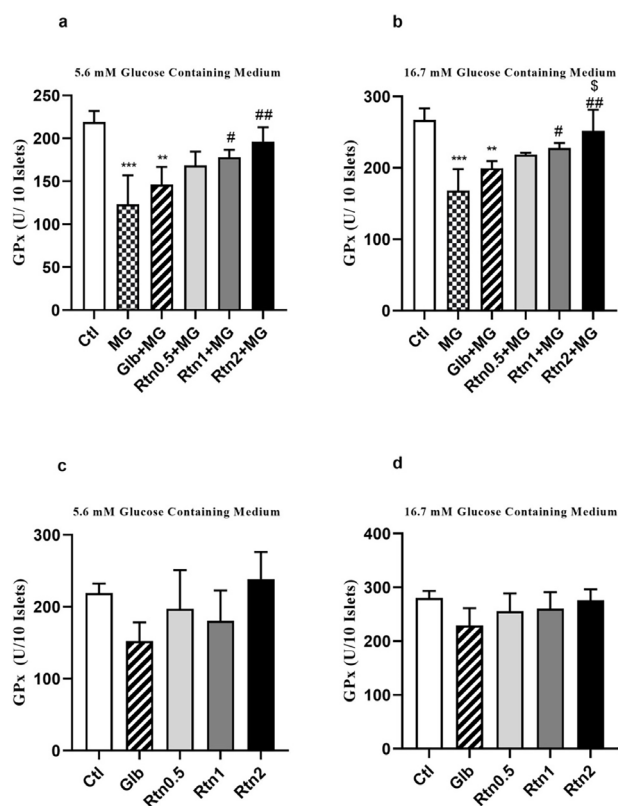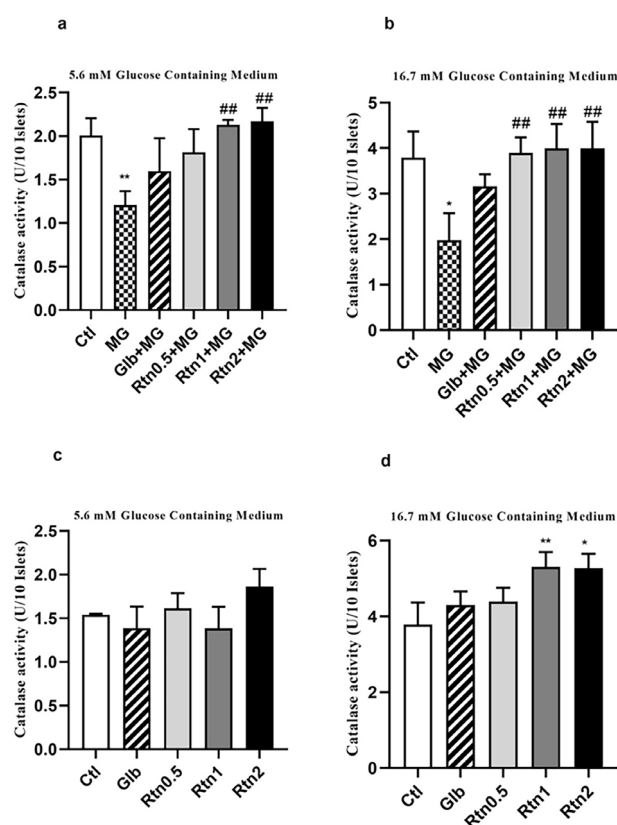

Figure 4. Effects of rutin on CAT activity with (a,b) and without (c,d) MG. Data are represented as mean ± SD.

Compared with control; # compared with MG. One symbol: $p<0.05$, two symbol: $p<0.01$, three symbol: $p<0.001$

hyperglycemic and antioxidant effects (19). Applying Rtn alone does not significantly alter beta islets when MG is present under normal conditions. Referring to these reports, Rtn seems to prevent lipid peroxidation in pancreatic beta-cells in MG-exposed islets. The present study is consistent with the previous results.

Previous research indicated that MG impaired β-cell function mainly by ROS generation, but the precise mechanism remains unknown. MG has been shown to decrease insulin secretion through the progression of apoptosis and suppression of β-cell function (12). According to these claims, MG induces OS and increases ROS, leading to impaired β-cell function. In the present study, the decreased insulin levels in hyperglycemic cultures were in line with the increase in lipid peroxidation in pancreatic β-cells. Rtn has a broad range of pharmacological effects. The ameliorative effects of Rtn on OS, inflammation, and apoptosis have been previously demonstrated (29,30). These reports corroborated our findings on the positive effect of Rtn on insulin secretion. Our results show that although Glb is a potent agent in insulin secretion from β-cells, the ability of Rtn, especially at high doses, to increase insulin levels appears to be greater in the presence of MG.

The activities of SOD, GPx, and CAT were decreased in islets exposed to 300 μM MG. Our results are in line with another report that demonstrated that MG depleted cellular antioxidants such as SOD, GPx, and CAT, resulting in damage to rat pancreatic β-cells (31). Intracellular antioxidants such as SOD, CAT, and GPx are crucial in protecting against OS-induced β-cells dysfunction (32). In accordance with our findings, Sun et al. (20) reported that Rtn not only increased the levels of CAT, GPx, and SOD but also decreased the MDA levels in streptozotocin-injected rats. Moreover, other previous studies have shown that Rtn protects hepatocytes from OS through excellent antioxidant capacity by enhancing the SOD, CAT, and GPx levels (18,30). High levels of intracellular or exogenous MG reduce the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of intracellular antioxidant levels (12,33). A previous *in vivo* study observed altered Nrf2 levels in MG-treated mice (34). Based on this document, it appears that MG influences Nrf2 levels. However, in this study, the impact of MG on reduced SOD, CAT, and GPx levels is probably related to this intracellular mechanism.

Study Limitations

This study, despite illustrating the protective effects of rutin against MG-induced pancreatic islet toxicity, contains several limitations. This study examined the short-term impacts of MG and rutin on oxidative stress and insulin secretion in isolated islet culture media, and it would be advantageous to explore the long-term effects of rutin on these parameters. Molecular investigations can enhance understanding of the fundamental mechanisms underlying rutin's effects.

CONCLUSION

The present study showed that Rtn, as a potent antioxidant, protects pancreatic islets by altering antioxidant levels in the presence of MG, and can be a pivotal bioactive compound for maintaining insulin secretion.

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Diagnostic Process of Adolescents with Abnormal Uterine Bleeding in Pediatric Departments: Single Center Results

Anormal Uterin Kanaması Olan Ergenlerin Tanı Süreci: Tek Merkez Sonuçları

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ABSTRACT

Objective: The present study aims to assess patients who applied to our hospital for abnormal uterine bleeding (AUB), and to examine the differences between cases diagnosed with hemostasis disorders and others.

Methods: This study prospectively included 105 patients who presented with AUB between 2021 and 2022. Complete blood count, peripheral blood smear, prothrombin time, activated partial thromboplastin time, fibrinogen level, thrombin time, von Willebrand factor antigen, ristocetin cofactor activity, factor VIII: C activity, flow cytometric analysis of platelet surface glycoproteins (Gp Ib/V/IX and Gp IIb/IIIa), biochemical assessments of iron status and blood group analyses, pelvic ultrasonographic imaging, and endocrine evaluations were conducted on the patients. The other factor tests were also assessed in cases with suspected hemostasis disorders.

Results: The mean age of the 105 patients included in the present study was found to be 15.3 (minimum: 11.3-maximum: 19.3) years. The most common etiology was ovulatory dysfunction in 55% (n=58) cases, followed by hemostasis disorders with 13.3% (n=14) cases, and genitourinary system infections with 9.5% cases. The level of deficiency was found to be mild in all cases with factor deficiency. The mean menarche-to-diagnosis time was determined to be 3.3 years for the patients with hemostasis disorders.

Conclusion: It is important to obtain detailed patient and family history, the menstrual history and physical examination of adolescent patients, and closely follow up on those having AUB for emergencies. Some patients' hemoglobin levels may decrease severely, and their hemodynamics may be impaired.

Keywords: Adolescents, blood disorders, abnormal uterine bleeding

ÖZ

Amaç: Bu çalışmanın amacı, anormal uterin kanama (AUK) nedeniyle hastanemize başvuran hastaları değerlendirmek ve hemostaz bozuklukları tanısı almış olgular ile diğerleri arasındaki farkları incelemektir.

Yöntemler: Bu çalışmaya 2021-2022 yılları arasında AUK ile başvuran 105 hasta prospektif olarak dahil edildi. Tam kan sayımı, periferik kan yayması, protrombin zamanı, aktive parsiyel tromboplastin zamanı, fibrinojen seviyesi, trombin zamanı, von Willebrand faktör antijeni, ristocetin kofaktör aktivitesi, faktör VIII: C aktivitesi, trombosit yüzey glikoproteinlerinin (Gp Ib/V/IX ve Gp IIb/IIIa) akım sitometrik analizi, demir durumunun biyokimyasal değerlendirmeleri ve kan grubu analizleri, pelvik ultrasonografik görüntüleme ve endokrin değerlendirmeleri hastalara yapıldı. Hemostaz bozukluklarından şüphelenilen olgularda diğer faktör testleri de değerlendirildi.

Bulgular: Çalışmaya dahil edilen 105 hastanın yaş ortalaması 15,3 (minimum: 11,3-maksimum: 19,3) yıl olarak bulundu. En sık etiyoloji %55 (n=58) olguda yumurtlama disfonksiyonuydu, bunu %13,3 (n=14) olgu ile hemostaz bozuklukları ve %9,5 olgu ile genitoüriner sistem enfeksiyonları izledi. Faktör eksikliği olan tüm olgularda eksiklik seviyesi hafif bulundu. Hemostaz bozukluğu olan hastalarda ortalama menarş-tanı süresi 3,3 yıl olarak belirlendi.

Sonuç: Ergen hastalarda ayrıntılı hasta ve aile öyküsü, adet öyküsü ve fizik muayene almak ve AUK olanların acil durumlar için yakın takibi önemlidir. Bazı hastaların hemoglobin seviyeleri ciddi şekilde düşebilir ve hemodinamikleri bozulabilir.

Anahtar Sözcükler: Ergenler, kan hastalıkları, anormal uterin kanama

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INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as abnormal bleeding from the uterine corpus from the aspects of bleeding duration, volume, frequency, and/or regularity (1). It is one of the urgent gynecological problems that are frequently encountered in adolescence and can cause concern. It was reported that 40% of healthy adolescents have had AUB at some point in their lives (2). AUB can lead to anemia, fatigue, and hemodynamic instability among adolescents, as well as other problems such as absenteeism from school, reduced quality of life, and falling behind in sports activities (3).

The American College of Obstetrics and Gynecology and the American Academy of Pediatrics defined normal menstruation as bleeding that occurs every 21-45 days, lasts less than 7 days, and does not require more than 3 pads or 6 tampons per day (4,5). Heavy menstrual bleeding is defined as bleeding that lasts longer than 7 days and/or blood loss of >80 mL per menstrual cycle, including the need to change pads every one to two hours, the use of two layers of tampons, staining bed or clothing, and the formation of clots larger than 2.5 cm (5,6). The International Federation of Gynecology and Obstetrics (FIGO) classified the causes of AUB into structural and non-structural categories (7). Structural causes include polyp, adenomyosis, leiomyoma, and malignancy (and hyperplasia) (PALM), while non-structural causes include coagulopathy, ovulatory disorders, endometrial, iatrogenic, and not otherwise classified (COEIN).

Structural AUB is seen very rarely in adolescents. The most common cause of AUB is the ovulatory dysfunction originating from the immaturity of the hypothalamic-pituitary-ovarian axis. Almost half of menstrual cycles are anovulatory for the first two years after menarche. The menstrual cycle interval narrows as age advances. In the 3rd year after menarche, the normal menstrual cycle is every 21-34 days, in 60-80% of cases. In addition, endocrinological causes such as thyroid diseases, hyperprolactinemia, hyperandrogenemia/polycystic ovary syndrome (PCOS), and obesity can cause ovulatory dysfunction. Pregnancy must also be considered for its impact and subsequently excluded where necessary. The patient should be examined for endometriosis and vulvovaginitis. The use of drugs, anticoagulants, or depot progesterone should be investigated. Moreover, trauma and foreign bodies are other causes of AUB (8).

Along with ovulatory dysfunction, coagulopathies also play an important role in the etiology of AUB. Previous studies reported that the frequency of underlying coagulopathies ranged between 8 and 62 % (9). It was shown that approximately 19% of adolescents requiring hospitalization due to excessive and prolonged menstrual bleeding (menorrhagia) have a coagulation disorder and more than 50% have a bleeding disorder, such as thrombocytopenia, von Willebrand disease, and leukemia (10). Von Willebrand disease is the most common hereditary bleeding disorder associated with AUB. The frequency of von Willebrand disease was reported to be 65% among women presenting with AUB (11). Factor XI deficiency, Glanzmann's thrombasthenia, and aplastic anemia are also associated with AUB. In 2010, the International Society on Thrombosis and Hemostasis (ISTH) developed a bleeding assessment tool (BAT) for the evaluation of patients with bleeding. Accordingly, ≥3 points were accepted as abnormal in children (12).

In this study, we aimed to assess adolescent patients who applied to our hospital with AUB, and to examine possible etiological factors.

MATERIALS AND METHODS

This study included 105 patients who applied to the pediatric hematology outpatient clinic between 2021 and 2022 for menstrual bleeding lasting longer than seven days, more frequent than a 21-day cycle, and increased blood loss in one cycle. Ethical approval (approval number: 2021/21-268, date: 06.12.2021) was obtained from the Erzurum City Hospital's Ethics Committee. The present study was carried out prospectively.

First of all, detailed anamnesis was obtained from the patients (items questioned are listed in Table 1), and this was done by performing a physical examination. No survey was conducted on quality of life, but some questions were asked about their school life and emotional state in the first assessment (Table 1). The assessments made after the anamnesis and physical examination are summarized in Figure 1. Platelet function tests and PFA-100/200 tests could not be conducted since they were not available.

The patients underwent endocrine evaluation for goiter and hyperandrogenemia, and were examined for vaginal infection. Thyroid function tests and βHCG levels were conducted to exclude pregnancy. Even though structural bleeding is seen very rarely in adolescents, pelvic ultrasonography was performed in all patients to rule out that condition. Patients were also examined for endometrial thickness and PCOS by pelvic ultrasonography. Ovulatory dysfunction was considered in patients if structural disorders and systemic diseases that could lead to vaginal bleeding were excluded. The cut-off values recommended by the World Health Organization were used when grading anemia (6.5-7.9, severe; 8-9.4, moderate; 9.5-10.9, mild; and >12, normal) (13).

The patients were also evaluated by using the ISTH-BAT scoring system.

According to this system:

0 point: Trivial

1 point: Consultation only or changing pads more frequently than every 2 hours or clot sand flooding or Pictorial Blood Assessment Chart Score >100

Table 1. Items evaluated when taking the anamnesis of the patients

Item
Age at presentation
Age at menarche
Bleeding duration and frequency
Additional complaints (vaginal discharge, dysuria, etc.)
Pad changing frequency
Presence of clot formation
Presence of another bleeding problem (post-dental treatment, ecchymosis in any body area, nose bleeding, etc.)
Presence of bleeding problem in family
History of related treatment (iron, tranexamic acid, or hormone)
History of related hospitalization (blood transfusion requirement)
Success in school, school absence, and emotional state

2 points: Time of work/school >2X year or requiring antifibrinolytic agents or hormonal therapy or iron therapy

3 points: Requiring combined with antifibrinolytic agents and hormonal therapy or present since menarche and >12 month

4 points: Acute menorrhagia requiring hospital admission and emergency treatment or blood transfusion or replacement agents or desmopressin. ISTH-BAT score of ≥3 is considered "abnormal" for children under 18 years old.

Patients were grouped by their menstrual bleeding patterns. Those who reported bleeding longer than seven days were considered to have long-term bleeding. Patients who had more than 80 mL of bleeding, needed to change pads every 1-2 hours, used baby/adult diapers, and had blood stains on their clothes or bedding were considered to have heavy menstrual bleeding. Moreover, patients who had bleeding more frequently than 21 days were included in the frequent menstrual bleeding group.

All coagulation factor levels were assessed according to the age reference values for children. The patients, whose factor levels were lower than the reference levels, were evaluated for a second time, but some of them did not attend their follow-up.

Statistical Analysis

"SPSS v.28.0 (IBM Corp., Armonk, NY, USA)" was used for statistical analyses. Descriptive statistics were used to characterize demographics, age at diagnosis, etiology of AUB, and bleeding episodes. Data were expressed as mean ± standard deviation and median (min., max.). Etiologies, hemoglobin measurement on admission, and patient characteristics were compared using the Mann-Whitney test for continuous variables and Pearson's chi-square test for categorical variables. The Kruskal-Wallis test was used when making comparisons between the groups. To compare age between two groups, Student's t-test was used. Correlation analysis was used to measure correlation between hemoglobin and quality of life. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the 105 patients included in this study was determined to be 14.27±1.86 years. Forty percent (n=42) of the cases were within the first year of menarche, and 60% (n=63) had been menstruating for more than one year. Sixty-six (62.9%), cases had complaints from the onset of menarche. The time since menarche was longer than one year in 12 patients with hemostasis disorders.

Classifying the cases by their menstrual bleeding episodes, it was determined that 50 patients (47.6%) had prolonged bleeding, 35 patients (33.3%) had heavy menstrual bleeding, and 20 patients (19%) had frequent bleeding. The most frequently noted bleeding episodes in patients with hemostasis disorders were prolonged bleeding (Table 2).

In 28.5% (n=30) of the cases, there was a history of bleeding problems other than menstrual bleeding. Sixteen patients had a family history of various bleeding problems. Only one of the patients with hemostasis disorders had a family history, and six patients had additional complaints, such as abnormal bleeding during tooth extraction, easy bruising, and nose bleeding. These complaints did not differ significantly in a statistical manner differ from those in the group without hemostasis disorders.

Using the ISTH-BAT scoring system, 62.9% (n=66) of the cases scored ≤2 points, 17.1% (n=18) 3 points, and 20% (n=21) 4 points. Nine patients with hemostasis disorders had a BAT score of 3-4 points, including 5 cases with von Willebrand disease, 2 cases with factor VII deficiency, 1 case with leukemia, and 1 case diagnosed with Glanzmann thrombasthenia. Examining the cases etiologically, it was found that the most common cause of AUB was ovulatory dysfunction originating from the immaturity of the hypothalamic-pituitary-ovarian axis, in 55% of the cases. In addition, hemostasis disorders were also responsible for AUB in 13.3% of the patients and were responsible for genitourinary system infections in 9.5% (Table 3).

Given the results obtained from pelvic ultrasonography imaging, three cases were diagnosed with PCOS, five cases with hemorrhagic ovarian cysts, and one case with an arcuate uterus.

1st
- Anamnesis ,Physical examination
- Complete blood count, prothrombin time, thrombin time, activated partial thromboplastin time, fibrinogen level, peripheral blood smear
- Urinalysis

2nd
- VWF antigen, ristocetin cofactor activity, and FVIII:C activity
- Pediatric endocrinology consultation
- Pediatric hematology consultation
- Pelvic ultrasonography

3rd
- Factor (II, V, VII, IX, X, XI, XIII)
- Flow cytometric analysis of platelet surface glycoproteins(glycoprotein Ib/IX/V and glycoprotein IIb/IIIa)

Figure 1. Patients evaluation algorithm

Table 2. Baseline characteristics of patients

	All (n=105)	With hemostasis disorders (n=14)	Without hemostasis disorders (n=91)	p
Age (years) (mean ± SD)	14.27±1.86	15.29±1.89	14.1±1.82	p=0.02
Time since menarche				p=0.12
<1 year	42 (40%)	2 (14.3%)	40 (43.9%)	
>1 year	63 (60%)	12 (85.7%)	51 (56.1%)	
Bleeding episodes				p=0.64
Prolonged	50 (47.6%)	8 (57.2%)	42 (46.2%)	
Heavy	35 (33.3%)	3 (21.4%)	32 (35.2%)	
Frequent	20 (19%)	3 (21.4%)	17 (18.6%)	
Other bleeding symptoms	30 (28.5%)	6 (43.8%)	24 (26.4%)	p=0.21
Family history	16 (15.2%)	1 (7.1%)	15 (16.5%)	p=0.69
ISTH-BAT score				p=0.11
≤2	66 (62.9%)	5 (35.7%)	61 (67%)	
3	18 (17.1%)	5 (35.7%)	13 (14.3%)	
4	21 (20%)	4 (28.6%)	17 (18.8%)	
Drug use history				p=0.57
Iron therapy	22 (20.9%)	2 (14.3%)	20 (21.9%)	
Oral contraseptive	15 (14.3%)	3 (21.4%)	12 (13%)	
Both (iron and oral contraceptive)	4 (3.8%)		4 (4.4%)	
Hemoglobin (g/dL) (median) (min-max)	12.9 (3.4-15.7)	12.5 (3.4-14.4)	12.9 (5-15.7)	p=0.37
Normal (>12)	73 (69.5%)	8 (57.1%)	65 (71.4%)	
Mild (9.5-10.9)	13 (12.4%)	2 (14.3%)	11 (12.1%)	
Moderate (8-9.4)	6 (5.7%)	2 (14.3%)	4 (4.4%)	
Severe (6.5-7.9)	13 (12.4%)	2 (14.3%)	11 (12.1%)	

SD: Standard deviation, ISTH: International Society on Thrombosis and Hemostasis, BAT: Bleeding assessment tool

Table 3. Causes of abnormal uterine bleeding

Cause	n (%)
Endocrinal causes	
Ovulatory dysfunction	58 (55)
Obesity	11 (10.5)
Hemorrhagic ovarian cyst	5 (4.8)
PCOS	3 (2.9)
Hypothyroidism	1 (0.9)
Hyperprolactinemia	1 (0.9)
Hematological causes	
von Willebrand disease	8 (7.6)
Factor VII deficiency	2 (1.9)
Factor XI deficiency	1 (0.9)
Factor V deficiency	1 (0.9)
Glanzmann thrombasthenia	1 (0.9)
Leukemia	1 (0.9)
Genitourinary system infections	10 (9.5)
Structural causes (arcuate uterus)	1 (0.9)
Other (celiac disease)	1 (0.9)

PCOS: Polycystic ovary syndrome

Von Willebrand disease was observed to be the most common hematological cause. The cases of von Willebrand disease were consistent with type-1 von Willebrand disease (vWF: /ratio of >0.6). The patients with other factor deficiencies also had mild deficiencies. Flow cytometric analysis of platelet surface glycoproteins (glycoprotein Ib/IX/V and glycoprotein IIb/IIIa) was conducted in 42 cases. One patient was diagnosed with Glanzmann thrombasthenia, whereas the remaining patients had normal results. Aggregometry tests could not be conducted. No platelet clustering was observed in the peripheral smear assessment of the patient with Glanzmann thrombasthenia.

Among the most common conditions causing ovulatory dysfunction, obesity was observed in 11 patients, PCOS in 3 patients, hypothyroidism in 1 patient, pituitary adenoma in 1 patient, and hyperprolactinemia in 1 patient. In addition, 1 patient had uncontrolled celiac disease.

Overall, the median hemoglobin concentration was 12.9 (3.4-15.7) g/dl. Thirteen (12.4%) patients had decreased hemoglobin levels, requiring a red blood cell transfusion. Eleven patients with severe anemia were not diagnosed with hemostasis disorder (Table 2). Forty-six (46.7%) patients stated that their quality of life was affected. There was a statistically significant correlation between hemoglobin levels and quality of life (correlation coefficient: -0.471). The

Gazi Med J 2025;36(2):184-191

Temuroğlu et al. Abnormal Uterine Bleeding

number of those whose quality of life was affected increased as the hemoglobin value decreased. Figure 2 illustrates the classification of the cases by hemoglobin levels.

None of the patients with factor deficiencies required factor therapy. The patients, who were found to be obese, were treated and followed up for obesity. The treatments applied to the cases are summarized in Figure 3.

Before admission to our outpatient clinic, 15 patients (14.3%) had a history of oral contraceptive use, 22 (21%) had a history of iron therapy, and 4 (3.8%) had a history of both. The frequency of bleeding diathesis was not increased in these patients. None of the patients used any drugs that could cause hemostasis disorders.

DISCUSSION

AUB has significant implications in adolescence since it causes a decrease in quality of life, an increased tendency to depression, and severe anemia that can be life-threatening. In addition, school absenteeism increases among adolescents with AUB, which results in a decrease in school success (3,14-18). It raises concern among both adolescents and their parents. Therefore, providing appropriate

medical treatment and psychological support is very important when adolescents present at the hospital due to AUB. In the present study, it was observed that school absences are high in these patients, and their emotional state is not good.

It is important to obtain a detailed menstrual history of adolescent AUB cases and investigate the presence of other bleeding problems, including easy bruising, nose bleeding, and post-surgical bleeding, which may indicate hemostasis disorders in those presenting with heavy bleeding, as well as the history of bleeding in the family (19). Given the detailed anamneses obtained in this study, there was a history of other bleeding disorders in 30 cases and a family history in 16 cases, for these cases. However, no statistically significant difference was found between patients with and without hemostasis disorders. This might be because of the few cases of hemostasis disorders.

Anovulatory bleeding is often seen in the first two years after menarche. In cases involving hemostasis disorders in this study, the time since menarche was longer than one year (mean: 3.3 years), and their complaints had been present since menarche. The patients generally complained of prolonged bleeding. Complications increase when patients cannot be diagnosed promptly.
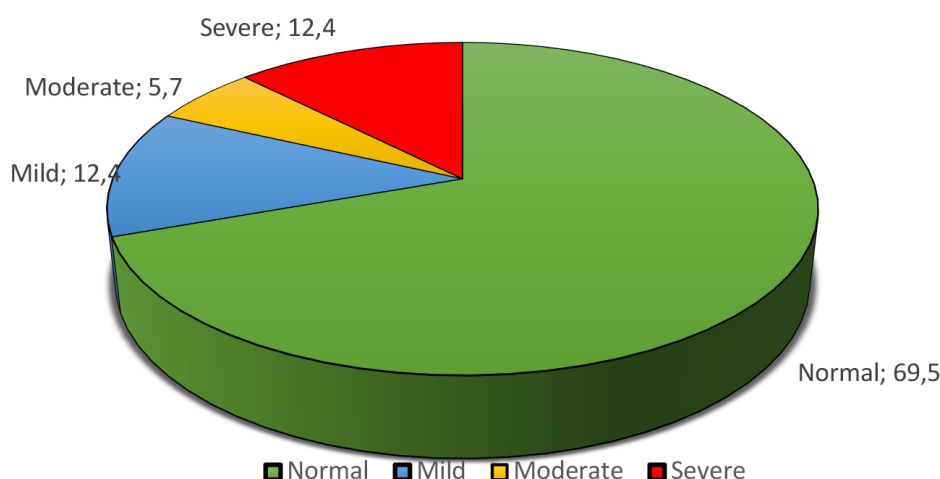

Figure 2. Classification of the cases according to anemia levels.
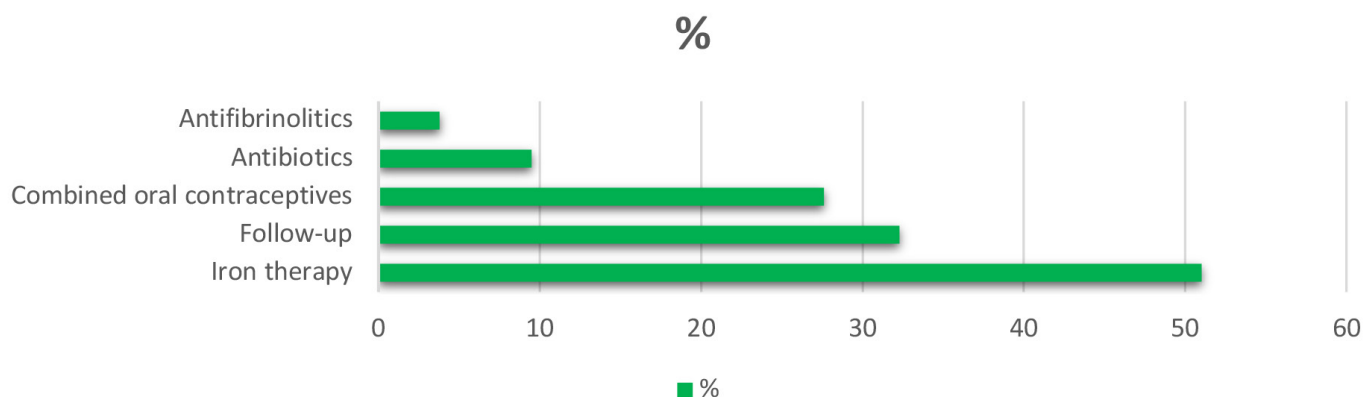

Figure 3. Treatments administered to the participating patients.

The FIGO classification was used for the evaluation of patients with AUB. Structural causes are less common among adolescents than adults. Anovulatory cycles originating from the immaturity of the hypothalamic-pituitary-ovarian axis in adolescents are the most common cause of AUB, but they are mainly considered when other diagnoses are excluded. On the other hand, PCOS and obesity can also lead to anovulatory cycles (20). Coagulopathies are the second-most frequent cause of AUB (21-26). In the present study, the most common etiological cause of AUB was anovulatory cycles, followed by mild factor deficiencies. Although platelet dysfunction is also common in cases of AUB (27-29), this diagnosis could not be made in the present study since this evaluation cannot be performed in our hospital. This can be considered a limitation of the present study.

The most common bleeding disorder in adolescents presenting with AUB is von Willebrand disease (30). Factor V, VII, and XI deficiencies were found in the patients with other factor deficiencies who were involved in this study. However, considering the difficult transportation conditions and the low education level in the geographical region where this study was carried out, it was not possible to follow up on these patients. The ISTH-BAT score is expected to be high in patients with coagulation problems (31). Most (n=9) of the participating patients with hemostasis disorders also had a high ISTH-BAT score. This scoring system can be used for distinguishing patients with bleeding susceptibility.

Performing routine pelvic ultrasonography on adolescent cases presenting with AUB remains controversial (32). However, although these conditions are not common among adolescents, pelvic ultrasonography is also important for detecting structural anomalies, endometrial thickness, and the presence of PCOS. Some hematological and solid tumor cases might have abnormal bleeding (33-37). None of the cases examined in this study had a diagnosis of solid tumors, but imaging can still be important. Patients with PCOS, hemorrhagic ovarian cysts, and structural anomalies might be diagnosed upon their admission to the hospital with the complaint of AUB (38). Eight of the patients participating in this study were diagnosed with PCOS, arcuate uterus, or hemorrhagic cysts, using ultrasonographic imaging.

Hematological malignancies might be present with AUB at the time of diagnosis, due to thrombocytopenia and coagulation disorders. Nebgen et al. (39) retrospectively evaluated 10,682 adult women with hematological malignancies and reported that the primary complaint was AUB in 38 cases at the time of admission. In the present study, one of the patients was diagnosed with acute myeloid leukemia.

Various studies aimed to demonstrate that hypothyroidism can cause delayed puberty and anovulatory cycles (40-43). However, it was observed that the incidence of hypothyroidism does not increase in cases with AUB (44,45). Hypothyroidism was found in only 1 patient participating in this study.

In a study carried out on adults, hyperprolactinemia was found in 17 of 105 patients with AUB (46). In the present study, the prolactin levels of the patients were within the normal range. Only one patient was followed up in the endocrinology department due to hyperprolactinemia and pituitary adenoma, and her prolactin level was normal.

The frequency of AUB in celiac disease is known to be higher when compared to healthy individuals, but the cause of this situation has not yet been clarified. It was considered that this might be due to the dysfunction of the hypothalamic-pituitary-ovarian axis (47). One of the cases involved in this study was monitored for a diagnosis of celiac disease, but it was determined that she did not comply with the recommended diet.

Since one of the most important complications of AUB is anemia, the complete blood count and iron parameters should be evaluated first while examining the patients with this complaint (48-50). Patients may present to the emergency department with severe anemia and encounter life-threatening situations. Therefore, cases with suspected anovulatory cycles should also be followed up closely. In a study carried out by Cooke et al. (49) the mean hemoglobin level of patients who applied to the emergency department with AUB was found to be 7.4 g/dL, which indicates severe anemia. Thirteen of the 105 patients involved in the present study had severe anemia that required a red blood cell transfusion. It was observed that the quality of life was worse for patients with anemia. Twenty-seven of the 73 cases with mild anemia had a history of using iron supplements and/or oral contraceptives before admission to our hospital. It was thought that these patients could have presented with more severe anemia without the use of such medications. It is important to obtain a detailed history of menstruation in adolescents presenting with anemia.

AUB treatment is based on stopping bleeding, relieving patient's concerns, maintaining the menstrual cycle, and treating anemia. Combined oral contraceptives, antifibrinolytics, iron replacement, and antibiotics (when necessary) are the most frequently used options. Iron replacement was started in more than half of our patients; oral contraceptives were started in approximately 30%. Red blood cell replacement was performed in severe anemia cases. The possibility of anovulatory bleeding was considered; and patients without anemia or heavy bleeding were followed up. In addition, antifibrinolytic therapy was administered to those who had factor deficiencies but did not require factor replacement.

CONCLUSION

Menstruation is a physiological event that develops under the influence of many factors. Many adolescents may not be willing to discuss their menstrual history for various reasons. Sufficient time should be allocated for these patients, and they should be followed up closely. It is important to obtain detailed patient's history, family history, menstrual history, and physical examination of adolescent patients. Cases with a history of hemostasis disorders should be referred to a hematology outpatient clinic. The patient's follow-up period and the timing of detailed examinations may vary between individuals. The majority of cases had abnormal bleeding in the anovulatory cycle; therefore, further examinations are unnecessary. However, as seen in the present study, anovulatory bleeding might reach life-threatening levels by causing severe anemia. To avoid unnecessary tests, the diagnosis process should be conducted step by step. Illustrating blood loss patterns in cases using pictured blood loss schemas might provide more objective results. If it is within the first year after menarche, if there is a bleeding history in the family, or if the bleeding reaches the level requiring hormone or iron

therapy, then further tests may be required. Even if they are rare, these malignancies should not be ignored.

Ethics

Ethics Committee Approval: Ethical approval (Approval number: 2021/21-268, date: 06.12.2021) was obtained from the Erzurum City Hospital's Ethics Committee.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., Concept: A.T., Design: A.T., E.D., Supervision: A.T., Resources: A.T., Material: A.T., Data Collection or Processing: A.T., A.Ö., E.D., Analysis or Interpretation: A.T., Literature Search: A.T., Writing: A.T., A.Ö., Critical Review: A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Perspectives on Listening to Music in the Operating Room Among Healthcare Professionals: A Cross-Sectional Study

Ameliyathanede Müzik Dinlemenin Sağlık Profesyonelleri Arasındaki Perspektifleri: Kesitsel Bir Çalışma

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ABSTRACT

Objective: To investigate the perspectives of healthcare professionals on listening to music in the operating room, considering their job satisfaction levels and the relationship between job satisfaction and music.

Methods: This cross-sectional study included 200 surgeons, anesthesiologists, and operating room nurses from three tertiary centers in Türkiye. Participants completed a survey consisting of demographic questions, general assessments of the appropriateness of listening to music in the operating room, and the Job Satisfaction Scale.

Results: The mean age of the participants was 39 years (standard deviation: +/- 11), with 59% female and 41% male participants. The majority of participants expressed positive opinions about listening to music in the operating room. The median score on the Job Satisfaction Scale for all volunteers was 20 (range: 5-25). A positive correlation was found between job satisfaction scores and favorable views on music (p<0.01, r=0.124). Conversely, increased professional experience was negatively correlated with positive perceptions of music (p=0.02, r=-0.165).

Conclusion: This study demonstrates that the majority of healthcare professionals hold positive views on listening to music in the operating room, with higher job satisfaction levels correlating with more favorable attitudes. Conversely, increased professional experience

ÖZ

Amaç: Sağlık profesyonellerinin ameliyathanede müzik dinleme konusundaki perspektiflerini ve iş tatmini seviyeleri ile müzik arasındaki ilişkiyi araştırmak.

Yöntemler: Bu kesitsel çalışma, Türkiye'deki üç üçüncü basamak merkezden 200 cerrah, anesteziyolog ve ameliyathane hemşiresini içermektedir. Katılımcılar, demografik sorular, ameliyathanede müzik dinlemenin uygunluğuna dair genel değerlendirmeler ve İş Tatmini Ölçeği içeren bir anketi tamamladılar.

Bulgular: Katılımcıların ortalama yaşı 39 (standart sapma: +/- 11) olup, %59'u kadın ve %41'i erkek katılımcılardan oluşmaktadır. Katılımcıların çoğunluğu, ameliyathanede müzik dinleme konusunda olumlu görüşler ifade etmiştir. Tüm gönüllüler için İş Tatmini Ölçeği'nde medyan skor 20 (aralık: 5-25) idi. İş tatmini puanları ile müzik hakkında olumlu görüşler arasında pozitif bir korelasyon bulunmuştur (p<0,05, r=0,124). Bununla birlikte, artan mesleki deneyim, müzik hakkındaki olumlu algılar ile negatif korelasyon göstermiştir (p=0,02, r=-0,165).

Sonuç: Çalışma, sağlık profesyonellerinin çoğunun ameliyathanede müzik dinleme konusunda olumlu görüşlere sahip olduğunu ve daha yüksek iş tatmini seviyelerinin daha olumlu tutumlarla ilişkili olduğunu göstermektedir. Ancak, daha deneyimli profesyoneller daha az olumlu görüşlere sahip olabilir. Bu bulgular, ameliyathanede müzik uygulanırken bireysel tercihlerin ve iş tatmininin dikkate alınması gerektiğini önermektedir. Müziğin cerrahi sonuçlar ve sağlık

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

ABSTRACT

tends to be associated with less positive perceptions of music during surgeries. These findings underscore the importance of tailoring music use in the operating room to individual preferences, considering both job satisfaction levels and professional experience. For instance, offering a choice of music or maintaining flexibility regarding its presence could enhance team morale and satisfaction. Additionally, institutions may consider periodic assessments of team preferences to balance the potential benefits of music with individual comfort levels. Further longitudinal research is recommended to assess the long-term effects of music on surgical outcomes, team dynamics, and healthcare professionals' well-being, ultimately guiding evidence-based implementation strategies in the operating room.

Keywords: Music, operation room, job satisfaction, surgery

ÖZ

çalışanlarının iyiliği üzerindeki uzun vadeli etkilerini keşfetmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Sözcükler: Müzik, ameliyathane, iş tatmini, cerrahi

INTRODUCTION

The impact of background music in the operating room has been a subject of research for many years. The use of music in the operating room was first introduced by Kane (1) with the aim of reducing patient anxiety. Since the 1930s, playing music for patients in the operating room has become a common practice to alleviate anxiety. Additionally, previous research has demonstrated that music's positive effects on anxiety reduction may be mediated through the hypothalamic-pituitary system, as shown by Conrad et al. (2).

From the perspective of healthcare professionals, the effect of music can vary based on experience, current psychological state, and other environmental factors. Music in the operating room can influence the team's communication, concentration, and individual performance. It has been shown that allowing individuals to choose the music can reduce stress levels and enhance performance (3). However, there are also reports indicating that music can negatively impact stress management, particularly for surgeons and anesthetists during critical moments (4,5).

Most studies on this topic have focused on the duration of the operation as the primary endpoint. Only one study has specifically examined how music in the operating room is perceived by anesthetists and nurses, as opposed to surgeons (6). However, this study only evaluated personal responses without considering the working conditions and job satisfaction of the staff.

Our study uniquely bridges this gap by evaluating the perspectives of healthcare professionals on listening to music in the operating room, while simultaneously assessing their job satisfaction levels. Unlike previous research, which has primarily focused on operation-related outcomes or isolated professional opinions, our study integrates both subjective perceptions and objective metrics, such as the Job Satisfaction Scale. This comprehensive approach enables us to better understand the interplay between environmental factors, individual preferences, and overall job satisfaction within the operating room setting.

MATERIALS AND METHODS

Our study was conducted simultaneously in three different tertiary centers in the same city in Türkiye. We planned to include 200 healthcare professionals in the study. This cross-sectional study involved surgeons, anesthesiologists, anesthesia technicians, and operating room nurses working in the fields of obstetrics and gynecology, urology, general surgery, orthopedics, otorhinolaryngology, cardiovascular surgery, and neurosurgery. Participants were included in the study regardless of age and gender. The study was carried out between September 1, 2023, and October 1, 2023, with healthcare personnel from the specified specialties who agreed to participate. Healthcare workers were informed about the study, and those who consented were included in the study after obtaining their approval. The ethics committee approval was obtained with the Lokman Hekim University Ethics Committee. (approval number: 2023/168, date: 20.09.20203). Healthcare workers were informed about the study, and those who consented were included in the study after obtaining their approval.

Participants were divided into three groups based on their specialties: surgeons (including specialists from obstetrics and gynecology, urology, general surgery, orthopedics, otorhinolaryngology, cardiovascular surgery, and neurosurgery), anesthesiologists (including anesthesia specialists and technicians), and operating room nurses. Only those who agreed to answer all the questions in the survey forms were included in the study. No healthcare worker refused to participate in the study.

Participants were asked to complete survey questions that could be answered in less than 3 minutes. Initially, 7 demographic questions were asked to investigate the distribution of the participants. The survey included a total of 11 questions rated on a 5-point Likert Scale. The first 6 questions were designed by the research team to evaluate the assessment of the appropriateness of listening to music in the operating room. These questions were based on our observations and literature review; however, no formal piloting process was conducted prior to their use. The last 5 questions were derived from the Job Satisfaction Scale. The short version of the Job Satisfaction Scale, consisting of five questions, was published in 1998, and its Turkish validation was published by Başol and Çömlekçi (8) The validated Turkish version was used in our study (7,8). The survey forms were collected on the same day they were distributed, and they were recorded anonymously. All questions in the survey form are provided in the appendix (Appendix 1).

Statistical Analysis

Data obtained from the study were analyzed using IBM SPSS Statistics 23 software. Descriptive statistics for normally distributed variables were reported using the mean and standard deviation, while non-normally distributed variables were reported using the

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

median and minimum-maximum. The normality of the variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Kruskal-Wallis test and Mann-Whitney U test were used to compare non-normally distributed multiple variables, and the Spearman correlation test was used for correlation analyses. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic data of the volunteers who participated in the study are presented in Table 1. The mean age of the participants was 39 years (standard deviation: +/- 11). Among the participants, 118 (59%) were female, and 82 (41%) were male. The median weekly working hours were 40 hours (min.-max.: 28-85), the median daily working hours were 8 hours (min.-max.: 4-11), and the median evening shift hours were 0 hours (min.-max.: 0-48).

The professional distribution of the participants was as follows: 50% (n=100) were surgeons, 25% (n=50) were anesthetists, and 25% (n=50) were nurses. When age, professional experience, weekly working hours, evening shift hours, and hospital bed capacity were grouped by profession, no significant differences were found among the professional groups (p>0.05, Table 1).

The distribution of responses to the survey questions by profession is presented in Table 2. For the first three questions, which positively assessed the effect of music in the operating room, a high percentage of participants responded with "agree" or "strongly agree" (87.5% for Question 1, 72.5% for Question 2, and 83.5% for Question 3, respectively).

The Job Satisfaction Scale questions and the responses provided by the participants are shown in Table 3. Questions 3 and 5 on the scale were reverse-scored. When the responses to the scale were scored, the median score for all volunteers was 20 (range: 5-25). The correlation between Job Satisfaction Scale scores and perspectives on music was evaluated, and all correlation results are presented in

Table 1. Basic characteristics of the professional groups participating in the study

			n	(%)
Age (years)	Surgeons	20-29	23	23
		30-39	30	30
		40-49	20	20
		50-59	20	20
		60-69	7	7
	Anesthesiologists	20-29	15	30
		30-39	21	42
		40-49	12	24
		50-59	2	4
		60-69	0	0
	Nurses	20-29	9	18
		30-39	12	24
		40-49	21	42
		50-59	7	14
		60-69	1	2

Table 1. Continued

			n	(%)
Years of professional experience	Surgeons	≤5	33	33
		≤10	9	9
		≤20	21	21
		>20	37	37
	Anesthesiologists	≤5	16	32
		≤10	5	10
		≤20	20	40
		>20	9	18
	Nurses	≤5	7	14
		≤10	7	14
		≤20	15	30
		>20	21	42
Weekly working hours	Surgeons	≤40	57	57
		41-50	25	25
		51-60	13	13
		>60	5	5
	Anesthesiologists	≤40	34	68
		41-50	7	14
		51-60	9	18
		>60	0	0
	Nurses	≤40	39	78
		41-50	6	12
		51-60	5	10
		>60	0	0
Number of weekly evening shifts	Surgeons	None	72	72
		1 shift	5	5
		2 shift	13	13
		≥3 shift	10	10
	Anesthesiologists	None	35	70
		1 shift	9	18
		2 shift	5	10
		≥3 shift	1	2
	Nurses	None	42	84
		1 shift	2	4
		2 shift	5	10
		≥3 shift	1	2
Hospital bed capacity	Surgeons	<250	28	28
		250-500	27	27
		>500	45	45
	Anesthesiologists	<250	10	20
		250-500	20	40
		>500	20	40
	Nurses	<250	8	16
		250-500	16	32
		>500	26	52

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

Table 4. A positive correlation was found between job satisfaction scores and the perceived positive effects of music in the operating room, while a negative correlation was observed with the perceived negative effects of music.

When analyzing the correlation between working hours and responses to questions about the positive effects of music, a statistically significant, negative correlation was found between weekly working hours and job satisfaction (p=0.02; r=-0.165). When evaluating day and night shift hours separately, no statistically

significant correlation was found between daytime working hours and the Job Satisfaction Scale (p=0.129, r=0.124). However, a statistically significant, negative correlation was found between evening shift hours and the Job Satisfaction Scale (p=0.001; r=-0.228).

No statistically significant difference was found in responses to the questions based on gender (p>0.005). Similarly, no statistically significant differences were found in responses among the three professional groups of surgeons, anesthetists, and nurses (p>0.005).

Table 2. Comparison of perspectives on listening to music in the operating room by professions

	Strongly disagree n (%)	Disagree n (%)	No opinion n (%)	Agree n (%)	Strongly agree n (%)
Q1: It is appropriate to listen to music during the operation					
Total	4 (2%)	8 (4%)	13 (6.5%)	128 (64%)	47 (23.5%)
Surgeons	0	5 (5%)	5 (5%)	64 (64%)	26 (26%)
Anesthesiologists	0	1 (2%)	5 (10%)	36 (72%)	8 (16%)
Nurses	4 (8%)	2 (%4)	3 (6%)	28 (56%)	13 (26%)
Q2: Listening to music during the operation increases my focus on my work					
Total	6 (3%)	32 (16%)	17 (8.5%)	103 (51.5%)	42 (21%)
Surgeons	2 (22.2%)	14 (48.3%)	9 (60%)	50 (47.6%)	20 (47.6%)
Anesthesiologists	0	12 (24%)	4 (8%)	24 (48%)	10 (20%)
Nurses	4 (8%)	4 (8%)	3 (6%)	27 (54%)	12 (24%)
Q3: Listening to music during the operation calms me down					
Total	5 (2.5%)	18 (9%)	10 (5%)	110 (55%)	57 (28.5%)
Surgeons	1 (12.5%)	9 (52.9%)	5 (55.6%)	55 (51.4%)	25 (42.4%)
Anesthesiologists	0	6 (12%)	4 (8%)	23 (46%)	17 (34%)
Nurses	4 (8%)	2 (4%)	1 (2%)	27 (54%)	16 (32%)
Q4: Listening to music during the operation distracts me					
Total	42 (21%)	129 (64.5%)	6 (3%)	19 (9.5%)	4 (2%)
Surgeons	16 (37.2%)	65 (51.2%)	2 (50%)	11 (57.9%)	1 (14.3%)
Anesthesiologists	11 (22%)	31 (62%)	2 (4%)	6 (12%)	0
Nurses	15 (30%)	29 (58%)	1 (2%)	2 (4%)	3 (6%)
Q5: It is not safe for patients to listen to music during the operation					
Total	44 (22%)	129 (64.5%)	11 (5.5%)	12 (6%)	4 (2%)
Surgeons	23 (54.8%)	60 (48.4%)	4 (26.7%)	6 (42.9%)	2 (40%)
Anesthesiologists	7 (14%)	38 (76%)	2 (4%)	2 (4%)	1 (2%)
Nurses	12 (24%)	28 (56%)	5 (10%)	4 (8%)	1 (2%)
Q6: Listening to music during the operation disrupts communication					
Total	28 (14%)	135 (67.5%)	10 (5%)	23 (11.5%)	4 (2%)
Surgeons	17 (63%)	60 (45.1%)	6 (60%)	12 (52.2%)	0
Anesthesiologists	3 (6%)	40 (80%)	2 (4%)	4 (8%)	1 (2%)
Nurses	7 (14%)	33 (66%)	1 (2%)	6 (12%)	3 (6%)

Q: Question

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

However, a significant difference was found between surgeons and anesthetists in response to the Job Satisfaction Scale question "Most days I am enthusiastic about my work" (p=0.03). Additionally, a significant difference was noted between surgeons and anesthetists for the question "I am often bored with my job" (p=0.02). A significant difference was also found between surgeons and nurses in response to the question "it is appropriate to listen to music during surgery" (80% vs. 72%, p=0.04).

When comparing perspectives on listening to music in the operating room with professional experience across all professional groups, a negative correlation was found between years of professional experience and questions indicating a positive view of music, while a positive correlation was found with questions indicating a negative view of music (Table 5).

DISCUSSION

Our study involved a total of 200 surgeons, anesthesiologists, and operating room nurses, conducted to investigate the perspectives of these professional groups on listening to music in the operating room, taking into account their job satisfaction levels. The results indicated that a majority of participants across all three professional groups expressed positive opinions about listening to music in the operating

Table 3. Comparison of job satisfaction scale by professions

	Strongly disagree n (%)	Disagree n (%)	No opinion n (%)	Agree n (%)	Strongly agree n (%)
1. I am quite satisfied with my current job					
Total	5 (2.5%)	13 (6.5%)	16 (8%)	128 (64%)	38 (19%)
Surgeons	3 (3%)	6 (6%)	5 (5%)	63 (63%)	23 (23%)
Anesthesiologists	2 (4%)	5 (10%)	4 (8%)	32 (64%)	7 (14%)
Nurses	0	2 (4%)	7 (14%)	33 (66%)	8 (16%)
2. Most days I go to work with enthusiasm					
Total	5 (2.5%)	23 (11.5%)	26 (14%)	116 (57.5%)	30 (14.5%)
Surgeons	2 (2%)	7 (7%)	12 (12%)	62 (62%)	17 (17%)
Anesthesiologists	3 (6%)	7 (14%)	9 (18%)	25 (50%)	6 (12%)
Nurses	0	9 (18%)	5 (10%)	29 (58%)	7 (14%)
3. Each day at work feels like it will never en					
Total	44 (22%)	118 (59%)	13 (6.5%)	20 (10%)	5 (2.5%)
Surgeons	24 (24%)	63 (63%)	5 (5%)	7 (7%)	1 (1%)
Anesthesiologists	7 (14%)	30 (60%)	4 (8%)	5 (10%)	4 (8%)
Nurses	13 (26%)	25 (50%)	4 (8%)	8 (16%)	0
4. I find my job funny					
Total	8 (4%)	16 (8%)	17 (8.5%)	133 (66.5%)	26 (13%)
Surgeons	2 (2%)	7 (7%)	6 (6%)	70 (70%)	15 (15%)
Anesthesiologists	4 (8%)	4 (8%)	3 (6%)	34 (68%)	5 (10%)
Nurses	2 (4%)	5 (10%)	8 (16%)	29 (58%)	6 (12%)
5. I think my job is unpleasant					
Total	52 (26%)	122 (61%)	8 (4%)	14 (7%)	4 (2%)
Surgeons	26 (26%)	63 (63%)	3 (3%)	7 (7%)	1 (1%)
Anesthesiologists	13 (26%)	28 (56%)	2 (4%)	4 (8%)	3 (6%)
Nurses	13 (26%)	31 (62%)	3 (6%)	3 (6%)	0

Table 4. Correlation between job satisfaction scores and perspectives on music

	Correlation coefficient (r)	p value
Q1: It is appropriate to listen to music during the operation	+0.102	**<0.001**
Q2: Listening to music during the operation increases my focus on my work	**+0.285**	**<0.001**
Q3: Listening to music during the operation calms me down	**+0.326**	**<0.001**
Q4: Listening to music during the operation distracts me	**-0.283**	**<0.001**
Q5: It is not safe for patients to listen to music during the operation	**-0.102**	**=0.001**
Q6: Listening to music during the operation disrupts communication	**-0.152**	**=0.003**

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

Table 5. Correlation between years of professional experience and perspectives on music

	Correlation coefficient (r)	p
Q1: It is appropriate to listen to music during the operation	-0.178	**=0.01**
Q2: Listening to music during the operation increases my focus on my work	**-0.242**	**=0.001**
Q3: Listening to music during the operation calms me down	**-0.207**	**=0.003**
Q4: Listening to music during the operation distracts me	**+0.183**	**=0.01**
Q5: It is not safe for patients to listen to music during the operation	**+0.174**	**=0.01**
Q6: Listening to music during the operation disrupts communication	**+0.176**	**=0.01**

room. We found that higher job satisfaction levels were associated with more positive emotions towards music in the operating room. Conversely, there was a negative relationship between increased work experience and positive perceptions of music, suggesting that more experienced healthcare professionals might have less favorable views on listening to music during operations.

These findings are consistent with the literature, where many studies have shown that listening to music during surgery leads to positive outcomes. Different studies have also demonstrated that healthcare workers hold positive views on listening to music in the operating room (9-11). Although it is difficult to attribute the preparation and completion time of surgery to a single external factor, prospective studies have reported that listening to music can positively impact reducing the duration of surgeries and the daily turnover time in operating rooms (12,13).

Our study did not find significant differences in perspectives on music among the professional groups, except for one question where nurses were more cautious about music in the operating room. Similar to our findings, other studies have reported that nurses tend to be more cautious than doctors about listening to music in the operating room, and women generally have a more positive attitude towards music than men (14). Additionally, our study found a negative correlation between increased professional experience and positive views on music, aligning with Hawksworth et al. (15) findings that older anesthesiologists felt music distracted them. These perspectives are influenced by personal factors and the participants' mood on the day they completed the survey. Therefore, larger-scale studies are needed to interpret these results more objectively.

Although various studies have examined factors such as profession, age, gender, professional experience, and music types, none have explored the impact of working conditions and job satisfaction on perspectives towards music. It is evident that job satisfaction, daily workload, and shift patterns directly affect responses. Our findings indicate that healthcare professionals with greater professional experience tend to hold less favorable views on listening to music in the operating room. This suggests that experienced staff may prioritize focus and concentration during procedures, potentially perceiving music as a distraction. Tailored interventions could address these concerns by offering options such as adjustable music volume, genre selection, or even silent periods during critical moments of surgery. Additionally, educational sessions or team discussions could help align preferences and create a balanced environment that respects individual needs while fostering team cohesion.

Contrary to our findings, Kurimoto et al. (16) reported that the job satisfaction of operating room nurses plateaued after 5-7 years and declined after 10 years. However, our study showed no relationship between professional years and job satisfaction. The work environment's impact on job satisfaction and adaptation is well-documented, and music can contribute to creating a positive environment and mood (16). Our study also found a positive correlation between job satisfaction and positive comments about listening to music, suggesting that music in the operating room can enhance job satisfaction and adaptation. Previous studies have shown significant relationships between working hours, job satisfaction scores, and adaptation (17). These findings suggest that music can contribute to healthcare workers' job satisfaction and potentially improve healthcare quality through appropriate music selection.

One limitation of our study is the cross-sectional design, which only provides a snapshot of the participants' perspectives at a single point in time. This design does not allow for the assessment of changes in attitudes over time or the establishment of causal relationships. Another limitation is the self-reported nature of the survey data, which may be subject to response biases, including social desirability bias. Additionally, the study was conducted in three tertiary centers within a single city, which may limit the generalizability of the findings to other regions or healthcare settings. Potential biases in our study must also be considered. Certain specialties, such as anesthesiology or surgery, might inherently prefer quieter environments due to the nature of their tasks and the need for concentration during critical moments. This could have influenced the overall perception of music's appropriateness and its reported effects. Future studies should explore these specialty-specific preferences in more detail to ensure a balanced approach to music implementation in operating rooms. Our study is limited by its geographic concentration, as it was conducted in three tertiary centers in a single city. Cultural factors, including societal norms and workplace traditions, might have played a significant role in shaping participants' attitudes toward music in the operating room. For instance, different regions may have varying tolerances or preferences for music in professional settings, potentially affecting the generalizability of our findings. Expanding this research to include diverse geographical and cultural contexts would provide a more comprehensive understanding of this phenomenon.

Despite these limitations, our study has several strengths. The inclusion of a diverse group of healthcare professionals, including surgeons, anesthesiologists, and nurses, allows for a comprehensive understanding of different perspectives on music in the operating room. The use of validated job satisfaction scales adds rigor to our assessment of the relationship between job satisfaction and attitudes towards music. Furthermore, the large sample size enhances the reliability of our findings.

Gazi Med J 2025;36(2):192-198

Sütcüoğlu et al. Music in the Operating Room

CONCLUSION

Our study indicates that the majority of healthcare professionals have positive views on listening to music in the operating room, with higher job satisfaction levels associated with more favorable attitudes. However, increased professional experience tends to correlate with less positive perceptions of music during surgeries. These findings highlight the importance of considering individual preferences and job satisfaction when implementing music in the operating room. Further research is needed to explore the underlying factors influencing these perspectives and to assess the long-term effects of music on surgical outcomes and healthcare workers' well-being. Our study suggests that appropriately selected music may enhance job satisfaction and potentially improve the quality of healthcare.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained with the Lokman Hekim University Ethics Committee. (approval number: 2023/168, date: 20.09.20203).

Informed Consent: Healthcare workers were informed about the study, and those who consented were included in the study after obtaining their approval.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.M.S., Concept: B.M.S., Z.C.Ü., S.A.E., Design: B.M.S., Z.C.Ü., S.A.E., Supervision: B.M.S., Resources: B.M.S., Material: B.M.S., Z.C.Ü., S.A.E., Data Collection or Processing: B.M.S., Z.C.Ü., S.A.E., Analysis or Interpretation: B.M.S., Z.C.Ü., S.A.E., Literature Search: B.M.S., Z.C.Ü., S.A.E., Writing: B.M.S., Z.C.Ü., S.A.E., Critical Review: B.M.S.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declare that there is no conflict of interest.

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Appendix I. A questionnaire administered to all participants

	Strongly Disagree	Disagree	No Opinion	Agree	Strongly Agree
Listening to music during surgery is appropriate					
Listening to music during surgery improves my focus on the task					
Listening to music during surgery helps me feel calmer					
Listening to music during surgery distracts me					
Listening to music during surgery is not safe for patients					
Listening to music during surgery disrupts communication					
I am very satisfied with my current job					
I go to work with enthusiasm on most days					
Every workday feels never-ending					
I find my job enjoyable					
I find my job unpleasant					

Exploring the Predictive Potential of Systemic Immune Inflammation Index and Hematologic Markers in Preterm Labor Risk Assessment

Preterm Doğum Riskinin Değerlendirilmesinde Sistemik İmmün Enflamasyon İndeksi ve Hematolojik Belirteçlerin Öngörü Potansiyelinin Araştırılması

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ABSTRACT

Objective: This study aimed to evaluate the potential association between the Systemic Immune Inflammation Index (SII) and preterm labor, given the growing interest in inflammatory biomarkers as possible predictors of pregnancy outcomes.

Methods: Conducted as a retrospective observational study at University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital, the study included 200 participants, split equally between those with preterm labor and a control group with term births. The study focused on singleton pregnancies, with the preterm group having gestational ages between 24 and 36+6 weeks; and the control group at 37 weeks or beyond. Hematological data, including SII, along with neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), were collected and compared across groups.

Results: Median SII values showed no significant differences between the preterm and control groups (727 vs. 740, p=0.642). Other inflammatory markers (NLR, PLR, and MLR) also displayed similar values in both groups. Notably, the preterm group exhibited lower gestational ages and birth weights compared to the control group (p<0.001). Cesarean delivery rates were significantly elevated in the preterm group (79%) relative to the control group (43%, p<0.001).

Conclusion: Although SII levels did not significantly differ between preterm and term births, the findings underscore the complex role of inflammation in preterm labor. Further research utilizing combined biomarker models may provide more precise risk assessment for preterm birth.

Keywords: Inflammatory biomarkers, neutrophil-to-lymphocyte ratio, preterm labor, Systemic Immune Inflammation Index

ÖZ

Amaç: Bu çalışma, Sistemik İmmün İnflamasyon İndeksi (SII) ile preterm doğum arasındaki olası ilişkiyi değerlendirmeyi amaçlamaktadır. Enflamatuar belirteçlerin gebelik sonuçlarını öngörmedeki potansiyel rolü giderek daha fazla ilgi görmektedir.

Yöntemler: Çalışma, Sağlık Bilimleri Üniversitesi, Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi'nde yürütülen retrospektif gözlemsel bir çalışmadır. Çalışmaya, 24-36+6 hafta gebelik süresine sahip preterm doğum yapan 100 kadın ve ≥37 hafta gebelik süresine sahip term doğum yapan 100 kadın olmak üzere toplam 200 katılımcı dahil edilmiştir. Hematolojik veriler, SII, nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve monosit-lenfosit oranı (MLR) gibi parametreler gruplar arasında karşılaştırılmıştır.

Bulgular: Medyan SII değerleri preterm ve kontrol grupları arasında anlamlı bir fark göstermemiştir (727 vs. 740, p=0,642). Diğer enflamatuvar belirteçler (NLR, PLR ve MLR) de her iki grupta benzer değerler göstermiştir. Ancak, preterm doğum grubunda gebelik haftası ve doğum ağırlığı belirgin şekilde daha düşük bulunmuş (p<0,001) ve sezaryen oranı anlamlı derecede daha yüksek olmuştur (%79 vs. %43, p<0,001).

Sonuç: SII seviyeleri preterm ve term doğumlar arasında belirgin bir fark göstermemiş olsa da, enflamasyonun preterm doğumdaki karmaşık rolü vurgulanmaktadır. Gelecekte, birden fazla biyomarkerin bir arada değerlendirildiği modellerin preterm doğum riskini öngörmede daha doğru sonuçlar sağlayabileceği düşünülmektedir.

Anahtar Sözcükler: Enflamatuvar belirteçler, nötrofil-lenfosit oranı, preterm doğum, Sistemik İmmün Enflamasyon İndeksi

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Gazi Med J 2025;36(2):199-203

Özkan and Üstün. Preterm Labor and Inflammatory Markers

INTRODUCTION

Preterm birth is a major perinatal issue, affecting an estimated 13.5 million births globally each year and accounting for approximately 10% of all deliveries. This condition not only poses immediate health risks to the neonate but also contributes to substantial morbidity and mortality rates, particularly in cases where preterm labor occurs spontaneously before 37 weeks of gestation (1,2). Among the complications associated with preterm birth, intrauterine inflammatory processes play a significant role, impacting neonatal health and survival through short-, medium-, and long-term complications (1,3). The wide range of neonatal medical treatments required and the associated costs, as well as the mortality and morbidity caused by preterm birth and the economic consequences, emphasize the importance of early detection and management of this critical perinatal condition.

Preterm labor has a multifactorial etiology. Pathologic, inflammatory and infectious factors, as well as fetal endocrine dysfunction, have been shown to contribute to susceptibility to preterm labor (4). The developing fetus, which is considered a semi-allograft, is not rejected by the immune system (5). Pro-inflammatory processes that occur during the first trimester of pregnancy facilitate migration of the blastocyst and support successful implantation. However, these inflammatory processes must remain in balance for successful implantation. Decreased levels of inflammation can lead to implantation failure, while excessive inflammation can lead to miscarriage (6,7). The increased inflammatory response associated with contractions during the first stage of labor and the inflammatory changes that occur in the cervix and myometrium support the role of inflammatory processes in the development of preterm labor (8,9).

Systemic inflammation can be measured with various biochemical and hematologic markers. Recent evidence suggests that measuring the ratio of cell types in blood, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), may provide prognostic and diagnostic insights for diseases associated with chronic low-grade inflammation (10,11). The systemic Immune Inflammation Index (SII) and delta-SII, new biomarkers of systemic inflammatory response based on peripheral blood cell counts, have been shown to be effective in predicting the prognosis of esophageal and cervical cancers as well as certain obstetric conditions such as intrahepatic cholestasis and fetal growth restriction in pregnancy (12-14). On the other hand, certain inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are associated with technical challenges and high costs in clinical practice, which limits their widespread use.

Although various biomarkers have been investigated to predict preterm labor and delivery, a cost-effective prediction model with sufficient sensitivity and specificity has not yet been developed. The aim of our study is to retrospectively investigate the association between SII and preterm labor by analyzing the hemogram parameters of patients who were diagnosed with preterm labor and hospitalized.

MATERIALS AND METHODS

Study Design

This retrospective observational cohort study was conducted at University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital. Patients diagnosed with preterm labor between January 1, 2016, and August 30, 2022, were included, allowing a comprehensive review of patient records over a 6-year period.

Study Population

The study included two groups: the preterm labor group, consisting of women with singleton pregnancies diagnosed with preterm labor between 24 and 36+6 weeks' gestation, and the control group, consisting of healthy women with singleton pregnancies who had delivered at term (≥37 weeks). Preterm labor was defined based on clinical signs and symptoms, including regular uterine contractions and cervical changes (dilatation and effacement) and, in some cases. The control group was selected by chronological matching of hospital records to ensure demographic similarity with the preterm labor group. A total of 100 patients were included in each group.

Inclusion and Exclusion Criteria

Women with singleton pregnancies who were diagnosed with preterm labor between 24 and 36+6 weeks were included in the study, and healthy women with singleton pregnancies who had delivered at term were included in the control group. Patients with chronic liver or kidney disease, autoimmune disease or chronic inflammation, infections such as urinary tract and respiratory tract infections, pelvic inflammatory disease, or coronavirus disease-2019, as well as those using corticosteroids or other anti-inflammatory drugs, were excluded. In addition, patients with suspected or confirmed chorioamnionitis, cardiovascular disease, or other conditions that could affect the white blood cell ratio or cause systemic inflammation were also excluded. Patients eligible for the control group were randomly selected based on hospital admissions during the same period as the preterm labor group.

Data Collection

Data were collected retrospectively from hospital records, including demographic information such as age, gravidity, parity, abortion history, Body Mass Index, and obstetric history. Hemogram parameters were also collected from blood samples taken at the time of admission for preterm labor or during routine visits for the control group. Complete blood count (CBC) was analyzed and hematological indices such as NLR, PLR, MLR, and SII were calculated. The SII was calculated using the following formula: (neutrophil count x platelet count)/ lymphocyte count. In addition, pregnancy outcomes were recorded, including gestational age at delivery, birth weight, type of delivery (vaginal or cesarean section), and neonatal outcomes.

Outcomes Definations

Primary Outcome: Predictive value of the SII for preterm labor: The primary outcome is to assess whether the SII can predict the occurrence of preterm labor.

Secondary outcomes: (1) neonatal birth outcomes, (2) gestational

age at birth: classified as preterm if the baby is delivered before 37 weeks' gestation. (3) birth weight: documented in grams at birth, (4) birth length: measured in centimeters at birth, (5) type of delivery: defined as vaginal delivery or cesarean section, with rates analyzed according to preterm delivery status. (6) additional inflammatory marker ratios: including NLR, PLR and MLR, which serve as secondary biomarkers of systemic inflammation and are compared between preterm and control groups.

Ethical Approval

This study was approved by the No 1 Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital (approval number: 14/07, date: 24.10.2022).

Statistical Analysis

The collected data were analyzed using SPSS version 23. Descriptive statistical methods included mean, standard deviation, and median. The distribution calculations was analyzed using the Shapiro-Wilk test. If a normal distribution was present, parametric tests (Student's t-test) were used. However, if no normal distribution was present, non-parametric tests (Mann-Whitney U test) were used to compare the groups.

RESULTS

The study included a total of 200 participants, divided equally between two groups: 100 individuals in the preterm labor group and 100 in the control group. The median age in the preterm labor group was 28.5 years [interquartile range (IQR): 24.0-34.0], which was significantly higher than the median age of 24.5 years (IQR: 21.0-28.0) observed in the control group ($p<0.001$) (Table 1).

The median SII values were computed for both groups, yielding 727 (IQR: 543-1032) in the preterm group and 740 (IQR: 603-965) in the control group, with no statistically meaningful difference between the groups ($p=0.642$). Additionally, analysis of other inflammatory markers, such as the NLR, PLR, and MLR, showed similar levels across both groups (NLR: $p=0.788$, PLR: $p=0.690$, MLR: $p=0.798$), indicating no significant variation in these parameters (Table 1).

The median gestational age at delivery was considerably shorter for the preterm labor group, recorded at 34 weeks (IQR: 33-35), as compared to 39 weeks (IQR: 38-40) in the control group ($p<0.001$). Birth weights also followed this trend, with a median of 2270 g (IQR: 1683-2615) in the preterm group, noticeably lower than the control group's median of 3325 g (IQR: 3000-3588) ($p<0.001$). Furthermore, delivery methods varied significantly, with a lower percentage of vaginal deliveries in the preterm labor group (21%) compared to the control group (57%), while cesarean delivery rates were higher among those in the preterm group (79% versus 43%, $p<0.001$). (Table 1).

DISCUSSION

This study investigated the relationship between the SII and preterm labor. Although the analysis showed no significant difference in SII scores between the preterm and control participants, our results indicate possible areas where hematologic markers such as NLR and PLR can be used as predictive indicators of preterm labor.

This is consistent with the existing literature, which has frequently emphasized the role of inflammatory markers in pregnancy outcomes. This warrants more comprehensive biomarker panels in future studies to capture the complexity of the inflammatory processes involved.

Preterm labor is a multifactorial condition in which inflammation plays a pivotal role. As previous studies have shown, inflammatory processes within the uterine environment may contribute to early labor onset by promoting contractions of the myometrium and structural changes in the cervix (15,16). In particular, the presence of infection and inflammation in placental tissue and fetal membranes has been consistently associated with an increased risk of preterm birth (17,18). Biomarkers such as IL-6 and TNF-α have been highlighted as key factors in this inflammatory response, as they are involved in signaling pathways that stimulate myometrial activity and cervical remodeling, essential components for the onset of labor (17,18).

The role of maternal blood biomarkers in predicting preterm birth continues to be an important area of investigation. In particular, studies on hematologic parameters have shown that certain metrics, such as NLR and PLR, have promising potential as low-cost, easily accessible tools for identifying systemic inflammation. Daglar et al. (19) found that MLR was significantly elevated in threatened preterm labor, which has important implications for clinical practice. In addition, a study by Ma et al. (20) showed that a combination of hemoglobin, platelet distribution width and NLR had high sensitivity and specificity for predicting preterm birth in asymptomatic women. These findings suggest that the combination of different inflammatory markers could provide a more comprehensive understanding of inflammatory status than single indices such as SII alone.

The results of this study are consistent with previous research highlighting the importance of inflammatory markers in preterm labor. However, the non-significant results in SII scores between preterm and control groups may be due to the different inflammatory pathways involved in the development of preterm labor, which could limit the diagnostic utility of a single inflammatory marker. Other systemic markers, such as CRP and IL-6, have been found to have different predictive power in different populations due to this heterogeneity in inflammatory responses (16,21).

Given the growing evidence for an association between inflammation and preterm labor, it is clear that isolating a single biomarker does not adequately capture the complexity of the disease. Instead, a composite biomarker approach, possibly incorporating NLR, PLR, and additional systemic inflammatory markers, may provide a more robust framework for identifying patients at risk of preterm labor (16,22). Such an approach could not only improve prediction accuracy but also provide a more individualized understanding of each patient's inflammatory profile, leading to more targeted treatment strategies.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design may introduce selection and information biases, potentially affecting the generalizability of the findings. Additionally, the sample size is relatively modest, which

Gazi Med J 2025;36(2):199-203

Özkan and Üstün. Preterm Labor and Inflammatory Markers

Table 1. Comparison of demographic, hematological, and pregnancy outcome variables between control and preterm groups

Variables	Control group (n=100)	Preterm labor group (n=100)	p
Age (years)	24.5 (21.0-28.0)	28.5 (24.0-34.0)	**<0.001**
Gravida			
median (Q_1-Q_3)	2 (1-3)	2 (1-3)	**0.039**
Min.-Max.	1-6	1-7	
Parity			
median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.034**
Min.-Max.	0-4	0-6	
Abortion			
median (Q1-Q3)	0 (0-0)	0 (0-0)	**0.764**
Min.-Max.	0-2	0-2	
Living child			
median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.037**
Min.-Max.	0-4	0-6	
Gestational week at admission	8 (7-9)	8 (7-9)	0.838
WBC (x10^3/uL)	8.65 (7.28-10.91)	8.81 (7.16-10.10)	0.549
RBC (x10^6/uL)	4.61±0.367	4.55±0.390	0.291
Hemoglobin (g/dL)	13.0 (12.4-13.5)	12.8 (11.8-13.6)	0.128
Hematocrit (%)	40.0±2.73	39.3±2.98	0.096
MCV (fL)	87.7 (85.0-90.5)	87.7 (83.3-91.0)	0.909
Platelets (x10^3/uL)	271 (236-310)	274 (226-321)	0.940
MPV (fL)	10.5 (9.9-11.4)	10.4 (9.9-11.4)	0.981
PCT (%)	0.29 (0.25-0.31)	0.28 (0.25-0.33)	0.774
Neutrophils (x10^3/uL)	5.86 (4.66-7.54)	5.97 (4.44-7.27)	0.517
Lymphocyte (x10^3/uL)	2.09 (1.72-2.46)	2.10 (1.66-2.47)	0.841
Monocyte (x10^3/uL)	0.61 (0.50-0.73)	0.59 (0.48-0.71)	0.419
Gestational week at delivery	39 (38-40)	34 (33-35)	**<0.001**
Birth length (cm)	51 (50-52)	43 (36-46)	**<0.001**
Birth weight (g)	3325 (3000-3588)	2270 (1683-2615)	**<0.001**
SII	740 (603-965)	727 (543-1032)	0.642
SIRI	1.65 (1.27-2.44)	1.59 (1.14-2.31)	0.508
PIV	477 (319-654)	425 (294-645)	0.603
PLR	132 (112-157)	134 (105-170)	0.690
MLR	0.274 (0.238-0.364)	0.281 (0.234-0.341)	0.798
NLR	2.80 (2.37-3.62)	2.83 (2.08-3.64)	0.788
Type of delivery			
Spontenous delivery	57 (57)	21 (21)	**<0.001**
Ceserean section	43 (43)	79 (79)	
Gender			
Female	52 (52)	53 (53)	N.A.
Male	48 (48)	47 (47)	

Statistical significance is indicated where applicable, with p-values less than 0.05 considered significant. Continuous variables are presented as medians with interquartile ranges (Q1-Q3) or means ± standard deviation, and categorical variables are shown as frequencies and percentages.
WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet count, MPV: Mean platelet volume, PCT: Plateletcrit, NEU: Neutrophil count; LYM: Lymphocyte count, MON: Monocyte count, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Prognostic inflammatory value; PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, Min.-Max.: Minimum-maximum, N.A.: Non-applicable

Gazi Med J 2025;36(2):199-203

Özkan and Üstün. Preterm Labor and Inflammatory Markers

may limit the power to detect subtle associations between systemic inflammatory markers and preterm labor. Another limitation is the reliance solely on hematologic parameters derived from CBCs; more comprehensive biomarker profiles, including cytokines and other specific inflammatory markers, were not available for analysis. The strength of our study lies in the use of a well-defined patient cohort, which allows for a more targeted analysis. Future research initiatives could expand the range of biomarkers and investigate the interactions between different inflammatory pathways associated with preterm labor in order to refine the predictive models and improve clinical applicability (17).

CONCLUSION

In conclusion, this study found no significant association between SII and the incidence of preterm labor. Nevertheless, our findings contribute to the growing body of evidence highlighting inflammation's crucial role in preterm labor pathogenesis. These results underscore the need for continued research into affordable, clinically applicable biomarkers that could better inform early interventions in preterm labor management. Moving forward, expanding the biomarker profile to include a combination of hematologic and inflammatory markers may offer more nuanced insights into identifying at-risk pregnancies, and support preventive healthcare practices.

Ethics

Ethics Committee Approval: This study was approved by the No 1 Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital (Approval number: 14/07, date: 24.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.Ö., Design: S.Ö., Supervision: Y.Ü., Data Collection or Processing: S.Ö., Y.Ü., Analysis or Interpretation: S.Ö., Literature Search: S.Ö., Y.Ü., Writing: S.Ö., Critical Review: Y.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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The Effect of Clinical Decision Support System on the Success of Respirative Syncytial Virus (RSV) Prophylaxis

Klinik Karar Destek Sisteminin Respiratuvar Sinsityal Virüs (RSV) Profilaksi Başarısı Üzerindeki Etkisi

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ABSTRACT

Objective: The aim was to examine the increase in the rate of respiratory syncytial virus (RSV) prophylaxis through a clinical decision support system (CDSS) added to the hospital information management system (HIS) and to determine the rate of increase before and after CDSS.

Methods: In October 2023, a CDSS was defined in HIS following the RSV prophylaxis indication protocol. To measure the effect of CDSS, and to determine the patients who need to receive RSV prophylaxis between 2021 and 2024, the drug reports registered on HIS were analyzed retrospectively with the code "B97.4- RSV, the causative agent of diseases classified in other sections," while the number of patients who started prophylaxis was recorded throughout three consecutive seasons.

Results: Thirty-one patients between 2021-2022, 42 patients between 2022-2023 and 68 patients between 2023-2024 were immunized by issuing a report for RSV prophylaxis. According to these data, while there was a 35% increase in the prophylaxis rate before CDSS compared to the previous season, after CDSS, there was an increase to 61%.

Conclusion: Systemic alerts added to hospital systems create significant differences in the treatment and follow-up of patients, considering the busy workload of healthcare professionals.

Keywords: RSV prophylaxis, palivizumab, clinical decision support system

ÖZ

Amaç: Hastane bilgi yönetim sistemine (HBYS) eklenen bir klinik karar destek sistemi (KKDS) aracılığıyla respiratuvar sinsityal virüs (RSV) profilaksisi oranındaki artışa bakılması ve KKDS öncesi ve sonrası artış oranının belirlenmesi amaçlanmıştır.

Yöntemler: Ekim 2023'te HBYS'ye RSV profilaksisi endikasyon protokolüne uygun olarak bir KKDS tanımlanmıştır. KKDS'nin etkisini ölçmek için 2021-2024 yılları arasında RSV profilaksisi alması gerekli hastaları belirlemek amacıyla HBYS üzerinde kayıtlı ilaç raporları "B97.4- RSV, diğer bölümlerde sınıflanmış hastalıkların etkeni" kodu ile retrospektif olarak belirlenip profilaksi başlanan hasta sayıları ardışık üç sezon boyunca kaydedilmiştir.

Bulgular: 2021-2022 yılları arasında 31 hasta, 2022-2023 yılları arasında 42 hasta, 2023-2024 yılları arasında 68 hastaya RSV profilaksisi için rapor çıkarılarak bağışıklanmıştır. Bu verilere göre KKDS öncesi profilaksi oranında bir önceki sezona göre %35'lik bir artış görülürken, KKDS sonrası bu artış oranı %61 olarak bulunmuştur.

Sonuç: Hastane sistemlerine eklenen sistemsel uyarılar sağlık profesyonellerinin yoğun iş temposu göz önüne alındığında hastaların tedavisi ve takibinde önemli farklar ortaya çıkarır.

Anahtar Sözcükler: RSV profilaksisi, palivizumab, klinik karar destek sistemi

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Gazi Med J 2025;36(2):204-207

Karkın Tozlu et al. Efect of Clinical Decision Support on Prophylaxis

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common viral cause of acute lower respiratory tract infection in infants (1,2). RSV causes a seasonal epidemic every year, and this epidemic lasts 5-6 months (October-March) (3).

RSV infection causes a significant increase in the mortality and morbidity of congenital heart diseases (CHD) (4). There is no specific treatment for RSV infection. Furthermore, RSV infection does not provide protection because it does not create permanent immunity. Therefore, identifying patients who need prophylaxis and immunizing them with the RSV monoclonal antibody palivizumab during the season reduces the mortality and morbidity of these patients (5). Immunization is administered at a dose of 15 mg/kg/dose once a month during the RSV season (6). In addition, immunization makes a significant contribution to the country's economy as it reduces the frequency and duration of hospitalizations and intensive care stays for patients.

In our study, we aimed to evaluate the change in the number of patients receiving prophylaxis through a clinical decision support system (CDSS) added to the hospital information management system (HIS). This system was designed to prevent patients suitable for RSV prophylaxis from being overlooked, due to intense workload, and to make immunization more efficient.

MATERIALS AND METHODS

Our study is single-centre. A CDSS, which was added to the HIS and tested on model patient samples, was used before the RSV season in 2023. A warning is displayed on the user screen when there is a patient entry suitable for RSV prophylaxis throughout the RSV season, starting from October 1st, delivered via the CDSS (Picture 1). In this way, the goal is to make RSV prophylaxis more efficient and systematic.

RSV prophylaxis indication criteria were determined according to the Turkish Pediatric Cardiology and Heart Surgery Association, palivizumab use recommendations for RSV prophylaxis guide (6). When creating the CDSS, age (<2 years), season (1 October-31 March), and international classification of diseases (ICD) codes meeting the criteria in the guide were used following the palivizumab use protocol. In case users do not use the ICD code for heart failure, the condition "if your patient has heart failure" was added to the algorithm for some ICD codes (e.g., Q21.1: atrial septal defect, Q21.2: atrioventricular septal defect) to check whether there is heart failure, and another warning was created as shown in Picture 2.

When patients suitable for the indications were determined, the ICD diagnosis code "B97.4- RSV, the causative agent of diseases classified in other sections" was entered, and an annual RSV prophylaxis report was prepared. It was planned to immunize patients monthly at 15 mg/kg/dose throughout the season.

Picture 1. Warning indicating the suitability of prophylaxis.

For patients who needed to receive RSV prophylaxis between October and March from 2021 to 2024, the drug reports registered on HIS were retrospectively scanned with the code "B97.4- RSV, the causative agent of diseases classified in other sections," and the number of patients for whom prophylaxis was initiated was determined.

The reports covering the seasons of two consecutive years were issued annually and recorded as singular, based on the first season in which they were issued. In this way, duplicate registration of the same patient was prevented.

Approval has been obtained from the Ethics Committee of Gazi University (approval number: E-77082166-604;01-1055541, date: 02.10.2024).

Data Collection and Statistics

The data were obtained as a result of a retrospective RSV prophylaxis drug report query, (with the code B97.4- RSV, the causative agent of diseases classified in other sections) through HIS between 2021 and 2024. The report was received from the hospital administration, in Excel format, without personal data, and was classified, with the classification including the start and end dates. Data were evaluated with the chi-square test.

RESULTS

From 2021 to 2024, a drug report was written for a total of 141 patients in our hospital within the scope of RSV prophylaxis eligibility. Thirty-one patients were detected in the 2021-2022 RSV prophylaxis season, 42 patients in the 2022-2023 season, and 68 patients in the 2023-2024 season (Figure 1). While the annual increase rate was 35% before the algorithm was added to HIS, it was observed that the annual increase rate reached 61% with the algorithm (p<0.001).
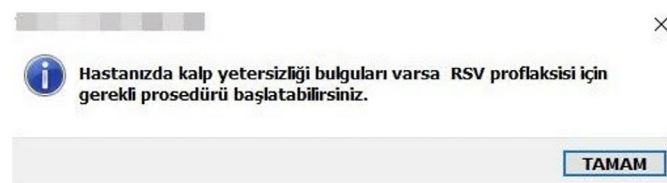
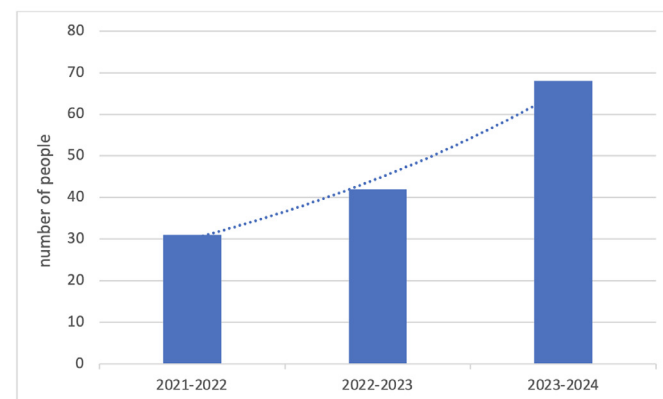**Picture 2.** Warning that makes you question heart failure.

Figure 1. Number of people receiving RSV prophylaxis by year.

RSV: Respiratory syncytial virus.

Gazi Med J 2025;36(2):204-207

Karkın Tozlu et al. Efect of Clinical Decision Support on Prophylaxis

DISCUSSION

The information systems used by hospitals play an important role in the follow-up, treatment of patients. CDSS installed on these information systems assist healthcare professionals in addressing these issues, providing warnings and alerts. We detected a significant increase in the rate of RSV prophylaxis with a simple algorithm that we defined in the HIS.

In the study conducted by Leone et al. (7), patients who needed to receive palivizumab were determined by looking at the diagnosis codes, oxygen needs, and medications taken from the patient files, and this immunization program was subsequently followed by an established team. The study observed that immunization increased by 78.4% in 2 years, and the importance of the correct entry of diagnosis codes, as well as a multidisciplinary approach, was emphasized. In our study, it is crucial to enter the diagnosis codes correctly. When the diagnoses in the CDSS algorithm are entered, warnings appear on the user screen. However, the diagnosis of heart failure often overlooked in the system. For this reason, another warning is added to the algorithm to remind the user that the diagnosis of heart failure is an indication of RSV prophylaxis. Thus, the referral of patients for prophylaxis has increased.

In a quality study conducted at the Children's Hospital of Philadelphia, palivizumab eligibility was determined when newborns were discharged from the ward. To determine this suitability, regular training was provided to the teams and the hospital pharmacist was also included in these training. A system was defined in the hospital software, and the patients identified by this team were directed, with a warning, for immunization when they returned to the hospital. The aim is to ensure that there is no deficiency in the patients' immunization doses (8). The patients we report for RSV prophylaxis include both outpatient and ward patients. Since the defined CDSS is available all users, a warning appears on the screens of all users (medical secretary, nurse, doctor) when registering patients suitable for prophylaxis. In this way, patient guidance is carried out in a versatile way.

In a study conducted by Lundeen et al. (9), automatic dosing for patients who meet palivizumab criteria has been approved through a program defined in the hospital system. Approval of consecutive doses has been accelerated in patients for whom medical evaluation was not performed each time, with the indication determined. Those with missing information were sent for medical examination, and the palivizumab dose was then decided. In addition, since current weights are recorded in this program, the appropriate dose is administered completely and immunization is carried out without wasting medication. Since our reports are issued annually, the patient does not need to be re-evaluated for RSV prophylaxis during the season. Immunization was ensured by measuring the weight of our patients at each visit and updating the dose.

Study Limitations

It is conceivable that the number of patients may be low during the coronavirus-19 (COVID-19) pandemic. However, during the COVID-19 pandemic, follow-up and treatment of serious diseases such as CHD continued without interruption.

The fact that a report is issued to the patients does not prove that prophylaxis was applied every month throughout the season.

While designing the algorithm, we used the CHD diagnoses that were most frequently entered during patient registration in HIS. We could not use ICD codes in the algorithm that were included in the guide, but could not be registered as a diagnosis in HIS. For this reason, the number of suitable patients we captured is less than our total number of patients. In addition, due to the incomplete entry of ICD codes, all conditions required for prophylaxis could not be queried using CDSS.

Conclusion

Systemic alerts added to hospital systems create significant differences in the treatment and follow-up of patients, considering the busy workload of healthcare professionals. We have developed this algorithm as an easy-to-understand, cost-free, and constantly usable application. With similar CDSS algorithms, healthcare workers can be reminded of the factors of chronic diseases that need to be monitored regularly, medical interventions or procedures that need to be performed annually, and drug doses that need to be repeated. We can make healthcare easier and more beneficial to our patients with simple measures.

Ethics

Ethics Committee Approval: Approval has been obtained from the Ethics Committee of Gazi University (approval number: E-77082166-604;01-1055541, date: 02.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.K., Design: S.K., Data Collection or Processing: G.K.T., Analysis or Interpretation: G.K.T., Literature Search: G.K.T., İ.B., Writing: G.K.T., İ.B., Critical Review: S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Nasopharyngeal Lipoma in an Adolescent Girl

Ergenlik Çağındaki Bir Kız Çocuğunda Nazofarengeal Lipom

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ABSTRACT

A benign nasopharyngeal mass typically presents with symptoms that may mimic those of chronic rhinosinusitis, such as nasal obstruction, rhinorrhea, and hyponasal speech. A nasopharyngeal mass that enlarges may extend into the oropharynx, resulting in symptoms, which may be more distressing, including foreign body sensation in the throat and choking sensation. We report a rare presentation of a nasopharyngeal mass that extended into the oropharynx in an adolescent girl, and turned out to be a nasopharyngeal lipoma. Despite a benign condition, the location of the mass, which results in distressing symptoms, requires intervention. We highlight the clinical presentation and management of this uncommon nasopharyngeal mass.

Keywords: Nasopharynx, lipoma, benign mass, nasal mass

ÖZ

Nazofarengeal benign bir kitle genellikle nazal obstrüksiyon, rinore ve hiponazal konuşma gibi kronik rinosinüziti taklit edebilen semptomlarla kendini gösterir. Büyüyen bir nazofarengeal kitle, orofarenkse uzanarak boğazda yabancı cisim hissi ve boğulma hissi gibi daha rahatsız edici semptomlara neden olabilir. Bu yazıda, bir ergen kızda orofarenkse uzanan nadir bir nazofarengeal kitle vakasını sunuyoruz ve bunun nazofarengeal lipom olduğu ortaya çıkmıştır. Her ne kadar benign bir durum olsa da, kitlenin yerleşimi rahatsız edici semptomlara yol açtığından müdahale gerektirmektedir. Bu nadir görülen nazofarengeal kitlenin klinik prezentasyonunu ve yönetimini vurguluyoruz.

Anahtar Sözcükler: Nazofarenks, lipom, benign kitle, nazal kitle

INTRODUCTION

Lipoma, albeit a common entity within the head and neck region, occurs rarely in the nasopharynx. Clinically, lipoma of the nasopharynx mimics other types of benign nasal masses, and imaging is usually required to aid in the diagnosis, although histopathological examination provides an accurate diagnosis. Patients remain asymptomatic throughout their lives owing to the slow-growing nature of the mass, although interestingly, patients may present with obstructive symptoms such as sleep apnoea. Previous studies have reported a peak incidence of nasopharyngeal lipoma in the 5th and 6th decades of life, while this condition is rarely seen in the first two decades of life (1,2). Herein, we report a rare case of benign lipomatous lesion of the nasopharynx in an adolescent girl.

CASE REPORT

A previously healthy 16-year-old girl presented with a 4-month history of halitosis and globus sensation. She occasionally feels like something is stuck in her throat. However, there are no dysphagia, odynophagia, or choking episodes. No constitutional or obstructive symptoms are present. Additionally, there were no recurrent nasal or throat symptoms.

Gazi Med J 2025;36(2):208-210

Musa et al. Nasopharyngeal Lipoma in An Adolescent Girl

Additionally, no other significant past surgical and family history was obtained. Upon examination, the patient was comfortable. Zero degree rigid nasoendoscopy revealed a pedunculated cystic mass with a stalk arising from the opening of the left eustachian tube, measuring approximately 2 cm x 2 cm. The bilateral osteomeatal complex was clear. Intraoral and otoscopic examinations were unremarkable. Other systemic examinations were normal.

Contrast-enhanced computed tomography revealed a non-enhancing pedunculated tubular lesion with cystic and fatty components, arising from the left nasopharyngeal region, measuring about 1.2 cm x 2.5 cm x 1.7 cm, without evidence of bony erosion and infiltrative features over the surrounding tissues, suggestive of benign fatty tissue. Magnetic resonance imaging (MRI) of the neck showed a high signal intensity T1-weighted lesion arising from the left nasopharyngeal wall, with a solid component peripherally (Figure 1).

Examination under anaesthesia and endoscopic excision of the nasopharynx mass was performed under general anaesthesia. Intraoperatively, the nasopharynx mass was excised using cold instruments, and histopathological examination of the mass revealed a stroma composed of fibrofatty tissue and skin adnexal, seen beneath the squamous epithelium, which was suggestive of a benign lipomatous lesion. Post-operatively, the patient was well with no complaints, and was symptom-free since then. Consent was obtained from the patient and the parent.

DISCUSSION

Lipomas are common benign soft tissue tumours encountered in all parts of the human body. They often occur in adults between 50 and 60 years old. Equal gender predominance was noted; however, some studies report male predominance (1,2). Individuals in their early 20s to 70 are rarely affected (1,2). Lipomas are composed of slow-growing mature adipose tissue and are rarely symptomatic.
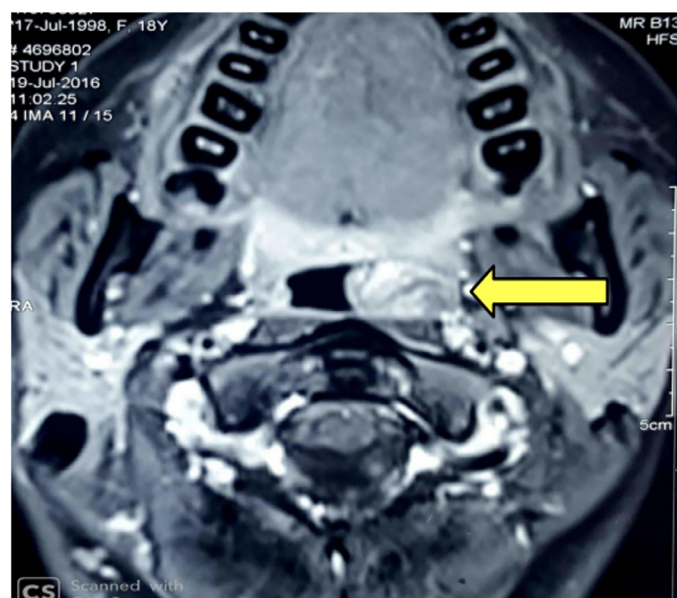

Figure 1. MRI shows high signal intensity T1W lesion arising from the left nasopharyngeal wall

MRI: Magnetic resonance imaging, T1W: T1-weighted

Localized effects on the surrounding tissue have been reported, resulting in large lipomatous lesions (1). Lipoma can occur in any part of the body, which contains fatty tissue. Based on previous data, the head and neck involvement of lipoma is nearly 30% and commonly involves the posterior triangle of the neck (1,2). Nasopharynx involvement of lipoma is considered rare due to the paucity of normal fatty tissue in that area (3).

Nasopharyngeal lipoma is characterised by a pedunculated or polypoidal mass (1,4,5), similar to our case. However, its clinical appearance can be mistaken for other common benign nasopharyngeal masses such as adenoid, antrochoanal polyp, inverted papilloma, pleomorphic adenoma, Thornwaldt's cyst, and vascular tumour. Hence, imaging plays a crucial role in guiding the clinician in making a definitive diagnosis and appropriate management of patients. Albeit rare, localised effects of nasopharyngeal lipoma include rhinorrhea, postnasal drip, nasal obstruction, epistaxis, anosmia, foul nasal odour, halitosis, palatal or retropharyngeal mass, foreign body sensation, dysphagia, hearing loss, aural fullness, voice change, cranial nerve involvement and meningitis (1-5). In our case, the lipomatous mass caused foreign body sensation and halitosis. MRI is the gold standard imaging technique given its higher resolution of soft tissue view (6,7). Computed tomography will demonstrate a homogeneous mass with low attenuation ranging from -65 to -120 HU with no evidence of enhancement and infiltrative features (8) as seen in our case. MRI will reveal strong signal intensity on T1 and T2 weighted images without any enhancement. Additionally, MRI can determine the margin of lipoma by delineating a "black rim" image, which distinguishes lipoma from the surrounding adipose tissue (7).

The main treatment for nasopharyngeal lipomas is surgical excision, aiming to bring a curative effect to cure the patient. However, lipomas that are deep-seated or close to vital structures may pose a challenge to surgeons. Interestingly, although not widely practised, some literature recommends postoperative radiotherapy in the case of incomplete resection or recurrence of symptomatic lipoma (1).

CONCLUSION

Nasopharyngeal lipoma, albeit a recherche, ought to be considered a differential diagnosis for a benign nasopharyngeal mass. Imaging, notably MRI, plays an important role in establishing the diagnosis. Complete surgical resection of lipomas is a gold standard treatment in all cases, and post-operative follow-up is important to ensure the absence of symptoms.

Ethics

Informed Consent: Consent was obtained from the patient and the parent.

Footnotes

Authorship Contributions

Concept: N.S.M., J.S., Design: N.S.M., J.S., Supervision: J.S., N.A.G., Resources: N.S.M., J.S., Material: N.S.M., J.S., Data Collection or Processing: N.S.M., J.S., Analysis or Interpretation: N.S.M., J.S., Literature Search: N.S.M., Writing: N.S.M., J.S., Critical Review: J.S., N.A.G.

Gazi Med J 2025;36(2):208-210

Musa et al. Nasopharyngeal Lipoma in An Adolescent Girl

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Paroxysmal Autonomic Instability with Dystonia (PAID) Syndrome: A Rare Occurrence

Distoni ile Paroksismal Otonomik İnstabilite (PAİD) Sendromu: Nadir Bir Olgu

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ABSTRACT

Paroxysmal autonomic instability with dystonia (PAID) is still under-recognized in clinical settings due to its rarity. This syndrome may mimic certain life-threatening conditions. We present a rare case of PAID syndrome. A 45-year-old female was brought to the hospital with an altered level of consciousness. An urgent computed tomography of the brain was performed, and a diagnosis of obstructive hydrocephalus secondary to cerebellar hemorrhage was made. Her family refused major surgery but consented to cerebrospinal fluid diversion. However, after several days in the ward, she developed ventriculitis. She was successfully treated with intravenous ceftriaxone. After several weeks at home, she developed episodic attacks of hypertension, tachycardia, and diaphoresis with hyperthermia and diaphoresis. She also had episodes of restlessness and generalized dystonic movements. She was diagnosed with PAID syndrome, and treatment was initiated. Her symptoms were successfully treated after three days.

Keywords: Paroxysmal autonomic instability with dystonia (PAID), dystonia, ventriculitis

ÖZ

Distoni ile paroksismal otonomik instabilite (PAİD), nadir görülmesi nedeniyle klinik ortamlarda hala yeterince tanınmamaktadır. Bu sendrom, belirli yaşamı tehdit eden durumları taklit edebilir. PAID sendromunun nadir görülen bir vakasını sunuyoruz. Kırk beş yaşında bir kadın, bilinç düzeyinde değişiklikle hastaneye getirildi. Acil beyin bilgisayarlı tomografisi çekildi ve serebellar hemorajiye bağlı obstrüktif hidrosefali tanısı konuldu. Ailesi büyük bir ameliyatı reddetti ancak beyin omurilik sıvısı yönlendirmesine razı oldu. Ancak koğuşta birkaç gün geçirdikten sonra ventrikülit geliştirdi. İntravenöz seftriakson ile başarılı bir şekilde tedavi edildi. Evde birkaç hafta geçirdikten sonra, hipertermi ve diyaforez ile birlikte hipertansiyon, taşikardi ve diyaforez atakları geliştirdi. Ayrıca huzursuzluk ve yaygın distonik hareketler atakları da yaşadı. PAID sendromu tanısı kondu ve tedaviye başlandı. Semptomları üç gün sonra başarıyla tedavi edildi.

Anahtar Sözcükler: Paroksismal otonomik dengesizlik ve distoni (PAID), distoni, ventrikülit

INTRODUCTION

The Autonomic Nervous System (ANS) is divided into two components, the parasympathetic and sympathetic nervous systems (1). The balance in this system fine-tunes the numerous voluntary and involuntary bodily processes in our body (2). However, there are some medical conditions that cause an imbalance in these systems, which include malignant hyperthermia, neuroleptic malignant syndrome, autonomic dysregulation and traumatic brain injury (3). Autonomic dysregulation (dysautonomia) can cause a complex physiological

picture, leading to imbalances in enteric, cardiac, motor, and respiratory systems. Paroxysmal autonomic instability with dystonia (PAID) is a subset of dysautonomia, which can mimic certain life-threatening conditions (4). PAID is a complex syndrome which is still under-recognised in clinical settings due to its rarity. We would like to present a case of PAID syndrome, information that could be very valuable for doctors around the world.

CASE REPORT

A 45-year-old female was brought to the hospital with altered level of consciousness. Before being brought in, she was complaining of severe headache and nausea. Her Glasgow Coma Scale was 7/15. An urgent computed tomography (CT) of the brain was done, and a diagnosis of obstructive hydrocephalus secondary to cerebellar hemorrhage was made. She was intubated and was on mechanical ventilation. Her family refused major surgery but consented for cerebrospinal fluid diversion. Her condition stabilized, but her recovery of consciousness with poor recovery in consciousness. Tracheostomy was done, and the patient was weaned off the ventilator.

However, after several days in the ward, she developed ventriculitis. The white cell count was raised (26,000 per microliter). Her blood culture and sensitivity revealed *Klebsiella pneumoniae*. Other blood parameters were normal. She was treated with intravenous ceftriaxone for one week. Her family was informed regarding the poor prognosis of the patient, and understood. She was referred to the rehabilitation unit before being discharged home.

However, after several weeks at home, she developed episodic attacks of hypertension, tachycardia, and diaphoresis with hyperthermia. She also had episodes of restlessness. According to her husband, the patient had generalized dystonic movements that resolved spontaneously after several minutes. These dystonic movements were increasing in frequency daily, with at least one attack.

Her blood investigations were normal, with no signs of infection. A repeat brain CT scan had no changes. After admission to the Neurosurgical Unit, the symptomatic management was commenced. She was given propranolol 10 mg three times a day via her nasogastric tube. She was also started on paracetamol, which helped her with the fever. Oral lorazepam was started to reduce her restlessness and dystonic movements. The patient responded well after two days into the treatment. She was discharged home after a week in the hospital.

DISCUSSION

PAID is sometimes seen among patients undergoing neuro-rehabilitation. This syndrome is often overlooked and misdiagnosed. Manifestations include arrhythmias, electrocardiographic alterations, hypohidrosis, increased intracranial pressure, neurogenic lung disease, and subnormal temperature in flaccid limbs. These are accompanied by dystonia of either rigidity, or decerebrate posturing during at least one episode per day for three consecutive days (2).

PAID is a complex syndrome and is difficult to diagnose. Understanding the pathophysiology is of utmost importance to diagnose and subsequently treat the syndrome. PAID is believed to be caused by altered actions of the hypothalamus, which interacts with the brainstem through a series of feedback loops and midbrain lesions.

This may lead to dystonia by interfering with normal inhibitory mechanisms, making patients tonically active and finally resulting in a hyperexcitable spinal reflex (2).

PAID syndrome appears to be a unique condition which usually follows brain injury. This syndrome may echo many life-threatening conditions. This would mean early recognition and management are very important. There may be a delay in initiation of subsequent management, which may cause an increase in morbidity among the affected patients. The differential diagnosis of PAID syndrome includes other clinical entities such as delirium tremens, sepsis, meningitis, dystonia, neuroleptic malignant syndrome, thyroid storm, and malignant hyperthermia. While most of these conditions can mimic PAID syndrome, the paroxysmal nature of symptoms such as autonomic activation, and generalised dystonia confirms the diagnosis of PAID (5).

The occurrence of episodes is always cyclical, with at least one episode per day. Due to the episodic nature of these manifestations, electroencephalography during an episodic attack will be difficult to obtain. The onset of these typical clinical signs generally occurs in the first week after brain injury and may persist for weeks or months, particularly in patients with a history of hypoxic brain injuries. Data have shown that 15% to 33% of patients develop PAID syndrome in the acute period after an insult to the brain (6). PAID syndrome complicates rehabilitation since it prolongs hospital stay. Morbidity is also increased, and an generally unfavourable functional outcome is expected (7).

The pathophysiology is still uncertain. It is speculated that PAID syndrome may be the result of the disinhibition or activation of central sympathetic excitatory regions located in the brain. These parts of the brain include the lateral periaqueductal grey substance, paraventricular hypothalamic nucleus, lateral parabrachial nucleus, and rostral ventricular medulla (8).

PAID is diagnosed based on specific criteria, which are shown in Table 1. PAID syndrome patients are usually free of symptoms or signs between the paroxysms. Malignant hyperthermia may also mimic PAID syndrome due to the hypermetabolic state, which happens after the patients have been given drugs such as non-depolarising agents and inhalational volatile agents (4).

Various medications have been used to manage PAID syndrome. However, there is no clear evidence that suggests that one medication regimen is better than another. After treating the underlying cause, adrenergic disinhibition has been successfully controlled with opiates such as morphine and dopamine agonists like bromocriptine. Additionally, benzodiazepines and baclofen

Table 1. Clinical criteria of PAID syndrome (5)

Criteria of PAID syndrome
• Temperature of more than 38.5 °C
• Hypertension
• Tachycardia of more than 130 beats per minute
• Respiratory rate of more than 40 breaths per minute
• Intermittent agitation (Rancho Los Amigos level ≤4)
• Diaphoresis
• Dystonia (rigidity or decerebrate posturing)

PAID: Paroxysmal autonomic instability with dystonia

have been used. The use of clonidine may also help to reduce blood pressure. Benzodiazepines, such as lorazepam, have sedating effects and muscle relaxant properties, which may help the patients during their uncontrolled symptoms (9).

It is important to know that withdrawal from opiate therapy may also provoke signs that falsely suggest PAID. The use of bromocriptine is effective in neuroleptic malignant syndrome, in which the clinical features suggest PAID. Dantrolene, on the other hand, has direct muscle relaxant properties and may reduce fever caused by prolonged muscle contraction, and also reduce the somato-sympathetic spinal reflexes that contribute to sympathetic excitation (5). Table 2 lists a review of commonly used medications and their uses in PAID syndrome.

The PAID manifestations observed in our patient only developed after the patient developed ventriculitis secondary to hydrocephalus. Ventriculitis may have caused the involvement of the midbrain structures. To the best of our knowledge, this is the first case report of PAID syndrome in association with Central Nervous System infection. PAID syndrome should be included as one of the differential diagnoses when a patient with similar signs and symptoms presents to the hospital. An early diagnosis and appropriate treatment can be established as soon as possible, thus reducing patient morbidity.

CONCLUSION

PAID can mimic a life-threatening condition. It is necessary to distinguish PAID syndrome from other conditions that can mimic it, such as sepsis, dystonia, delirium tremens, neuroleptic malignant syndrome, meningitis, and thyroid storm. Early diagnosis and treatment can lead to rapid recovery.

Table 2. Treatment guide for PAID syndrome

Symptoms	Medication
General symptoms	Morphine, labetalol/ Propanolol and gabapentin
Agitation	Lorazepam
Resistant hypertension & hyperthermia	Clonidine
Persistent dystonia or posturing	Dantrolene

PAID: Paroxysmal autonomic instability with dystonia

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Patellar Tendon Avulsion at the Tibial Tubercle at Subacute Stage: A Case Report

Subakut Evrede Tibial Tüberkül Seviyesinde Gelişen Patellar Tendon Avulsiyonu: Olgu Sunumu

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ABSTRACT

The objective of this case report is to present a rare case of patellar tendon avulsion at the tibial tubercle in a 12-year-old male patient and describe the surgical treatment and rehabilitation process. A 12-year-old male patient with an otherwise healthy status presented with a rupture of the patellar tendon without bony involvement after sustaining a knee injury during a soccer game. Treatment involved a combination of end-to-end suture, support with anchors, and patellar reinforcement using a cerclage wire, a unique approach not previously documented for the pediatric population. Early range of motion exercises were initiated with the use of a functional knee brace. The patient's progress was assessed through Lysholm and Kujala Scores, as well as a visual analog scale (VAS) for pain. At the final follow-up, conducted 6 months after the surgery, the patient showed satisfactory knee function, with Lysholm and Kujala scores of 85 and a VAS pain score of 0. Radiographic examinations confirmed the successful healing of the patellar tendon with full range of motion in the knee joint. Patellar tendon avulsion at the tibial tubercle is a rare injury in the pediatric population, requiring early diagnosis and prompt surgical treatment to preserve the extensor mechanism and prevent functional loss. The presented combination of end-to-end suture, cerclage wire reinforcement, and anchor support proved effective in this case. This report contributes valuable insights into the treatment of distal patellar tendon avulsion in pediatric patients and emphasizes the importance of appropriate management of such injuries to ensure optimal recovery and knee function. Further research and prospective studies are warranted to validate the efficacy of this surgical approach in larger cohorts.

Keywords: Adolescent, extensor mechanism, knee, patellar tendon, avulsion, sleeve, fracture

ÖZ

Bu olgu sunumunun amacı, 12 yaşında erkek bir hastada tibial tüberkül üzerinde patellar tendon avulsiyonunun nadir bir vakasını sunmak ve cerrahi tedavi ile rehabilitasyon sürecini açıklamaktır. Diğer sağlık durumu normal olan 12 yaşındaki erkek hasta, futbol maçı sırasında diz yaralanması sonucu kemik tutulum olmaksızın patellar tendon rüptürü ile başvurdu. Tedavi, uçtan uca sütür, ankor ile destek ve patellar güçlendirme için serklaj teli kullanımı gibi pediatrik popülasyon için daha önce belgelenmemiş, özgün bir yaklaşım içeriyordu. Erken dönem hareket açıklığı egzersizlerine, fonksiyonel diz ateli kullanılarak başlanmıştır. Hastanın ilerlemesi, Lysholm ve Kujala Skorları ile ağrı için görsel analog skala (VAS) ile değerlendirildi. Ameliyat sonrası 6 ay sonra yapılan son takipte hasta, Lysholm ve Kujala skorları 85 ve VAS ağrı skoru 0 ile tatmin edici diz fonksiyonu gösterdi. Radyografik ve fiziksel incelemeler, patellar tendonun tam iyileşmesini ve diz ekleminde tam hareket açıklığını doğruladı. Patellar tendon avulsiyonu, pediatrik popülasyonda nadir bir yaralanma olup, ekstansör mekanizmanın korunması ve fonksiyon kaybının önlenmesi için erken tanı ve acil cerrahi tedavi gerektirir. Sunulan uçtan uca sütür, cerclaj teli ile güçlendirme ve ankraj desteği kombinasyonu bu vakada etkili olmuştur. Bu rapor, pediatrik hastalarda distal patellar tendon avulsiyonunun tedavisi hakkında değerli bilgiler sunmakta ve bu tür yaralanmaların uygun yönetiminin optimal iyileşme ve diz fonksiyonu sağlama açısından önemini vurgulamaktadır. Daha geniş kohortlarda bu cerrahi yaklaşımın etkinliğini doğrulamak için daha fazla araştırma ve prospektif çalışmalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Adölesan, ekstansör mekanizma, diz, patellar tendon, avulsiyon, sleeve, fraktür

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Gazi Med J 2025;36(2):214-217

Özer et al. Subacute Patellar Tendon Avulsion in a Child

INTRODUCTION

Complete extensor mechanism injuries are rare conditions in the pediatric population. However, participation in sports at a younger age exposes individuals to injuries of the musculoskeletal system. Patellar tendon injury makes up 3% of all extensor mechanism problems. Aseptic conditions such as Sinding-Larsen-Johanson's disease and Osgood-Schlatter's disease predispose severe patellar tendon injuries in adolescents. Patellar tendon rupture is rarer, with an incidence of 0.68 per 100,000 people. It usually occurs in male adults over the age of 40 (1). It has been reported in 7% of pediatric patients. Patellar tendon rupture usually occurs in the proximal insertion region in mature adolescents, and tibial tubercle avulsion injuries are rare in the pediatric population (2). The limited number of cases of distal patellar tendon rupture described in the literature has been reported in adults, and most of them are associated with additional intra-articular lesions (anterior cruciate ligament and medial collateral ligament tears, meniscal damage) (2-4). To our knowledge, there are few publications in the literature that report on the treatment and outcomes after distal patellar tendon avulsion in the pediatric population (5,6). Although distal patellar tendon avulsion is rare in the pediatric population, it can cause serious problems such as knee pain and loss of function in the extension mechanism. Therefore, it is important to be aware of these injuries. We describe here a case of patellar tendon avulsion at the tibial tubercle, with a fleck of bone acting as a sleeve from the epiphyseal bone of the proximal tibia, and its surgical treatment.

CASE REPORT

A 12-year-old male patient was admitted to our outpatient clinic with complaints of swelling and loss of knee extension after sustaining a knee injury 9 days prior to his visit during a soccer game. There was a gross hematoma, and he was unable to extend his knee due to the pain on the anterior aspect of the knee. On his x-rays, the right patella had migrated cranially, while the contralateral patella sat in its anatomically correct position (Figure 1). Magnetic resonance imaging revealed disruption of the patellar tendon at the tibial tuberosity (Figure 2). Although there was no sign of fracture at the tibial tuberosity, Osgood-Schlatter sign was visible on plain x-rays bilaterally. The Lysholm Score was 35, Kujala Score was 26, and VAS pain score was 4 before the surgery. Surgery was performed after confirming the pure avulsion at the tuberosity via magnetic resonance imaging. During surgery, a small flake of epiphyseal bone attached to the patellar tendon was observed. Cerclage wire was
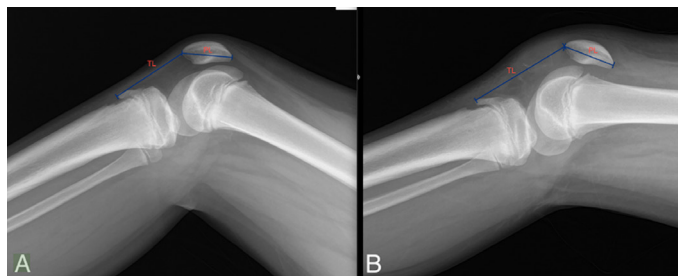
used during the approximation of the tendon to the tuberosity, while augmented polyethylene sutures with 2 footprint anchors (FOOTPRINT Ultra PK, Smith & Nephew, USA) were used to repair the tendon to the tuberosity medially and laterally (Figure 3). The knee was immobilized with an angle-adjustable knee brace set to keep the joint at full extension for 6 weeks, and the brace was removed for passive exercises. Brace was taken off at 12 weeks. The cerclage wires remained, and the control radiographs and physical examination showed successful healing of the tendon with full range of motion of the knee joint (Figure 4). The immediate postoperative
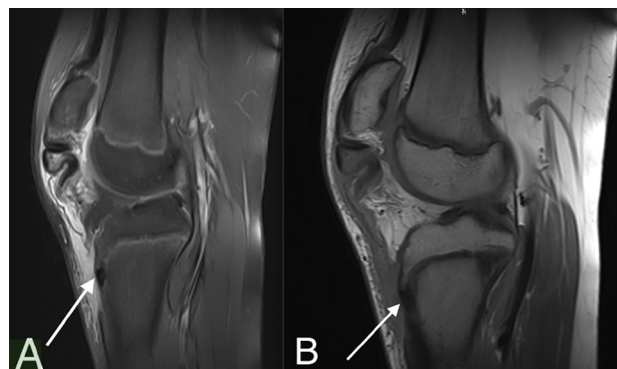
Figure 2. Preoperative (A) T2 weighted; (B) T1 weighted magnetic resonance images of the affected knee showing complete rupture of patellar tendon from the tibial tuberosity
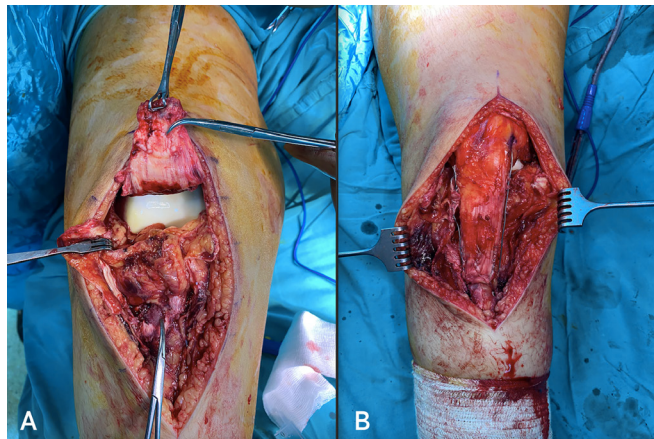
Figure 3. Intra-operative photographs showing (A) a ruptured patellar tendon, (B) end-to-end suture of ruptured tendon and reinforcement of patella with a cerclage wire

Figure 1. Preoperative x-ray of the (A) healthy knee; (B) affected knee showing considerable increase in tendon length (TL) and increased Insall-Salvati ratio of 1.89 (tendon length divided by the patellar length (PL) for the affected knee

Figure 4. Postoperative radiographs showing decreased tendon length and return of patella to its anatomical site

Gazi Med J 2025;36(2):214-217

Özer et al. Subacute Patellar Tendon Avulsion in a Child

range of motion of the knee is demonstrated in Supplementary Video 1. At months follow-up, Lysholm and Kujala Scores were 85 and VAS pain score was 0.

Rehabilitation

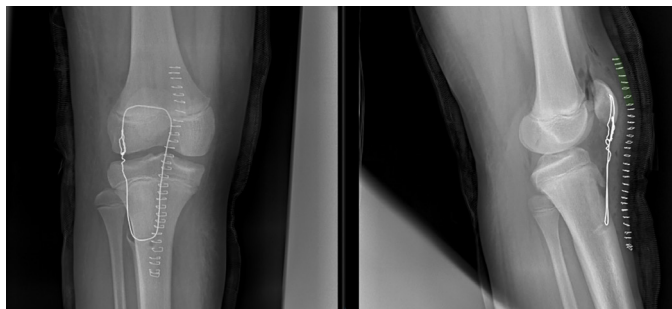Rehabilitation started immediately after the surgery. Full passive knee flexion and extension exercises isometric knee extension and hip abduction and adduction exercises were started immediately. Active-assisted knee extension exercise was started after 3 weeks and active knee extension was allowed after 6 weeks. Toe-touch weight-bearing with crutches was allowed after the third week postoperatively. Weight-bearing as tolerated was allowed 6 weeks after the surgery, and full weight bearing without crutches and a brace was allowed 12 weeks postoperatively. Sports-specific exercises were started gradually, and athletes returned to sports at 6 months.

DISCUSSION

Patellar tendon ruptures, common in the 3rd and 4th being the injuries of 3rd and 4th decade of life are rarely seen in the pediatric population and can be isolated, involve the inferior patellar pole or with accompanying tibial tubercle avulsion. Frequency of sustained patellar tendon injuries in children has increased with the rise of popularity of sports and recreational activities. The mechanism behind this injury is believed to be the increased strain on the tendon due to the forced extension of the knee while the leg is flexed (7).

Although the condition is rare, early diagnosis is necessary to provide the needed treatment as soon as possible, avoid functional loss in the future, and preserve the extensor mechanism. Early diagnosis may be hindered by acute swelling and pain, and delayed diagnosis there will be need for more complicated surgical methods (8). Radiological tools could be used to aid the diagnosis.

For the partial ruptures of patellar tendon, non-operative methods such as bracing may be used. In cases of total rupture and disruption of the extensor mechanism, operative techniques such as primary end-to-end repair should be used. Reconstruction with a tendon allograft is reserved for chronic conditions where ruptured ends could not be brought together (9). In the available literature, for the treatment of acute and subacute patellar tendon rupture, the use of the Krakow technique and anchoring, is endorsed, and a cerclage wire or a polydioxanone suture may be used to further stabilize the patella. The use of end-to-end suture and fixation of the patella with cerclage wire was reported to have satisfactory outcomes postoperatively in traumatic patellar tendon rupture without bony involvement (5). As Bushnell et al. (10) reported, using a suture anchor technique in primary repair improved the functional outcome considerably, but due to the lack of data for the comparison of methods, there might be a need for randomized trials. Usage of cerclage wire may benefit the outcome of the operation by providing stability for the patella and further security for primary sutures and footprint anchors used, when compared to other options. According to the tests conducted by İyigün et al. (11) support with a wire was shown to provide the most biomechanical support compared to other methods. Disadvantages of this procedure include a need for reoperation to remove the wire (12).

Additionally, Ravalin et al. (13) recommend the use of patellar tendon augmentation to decrease the risk of gap formation at the healing site, which, if formed, may lead to clinical failure and extensor mechanism lag. With patellar tendon augmentation, the patient may be mobilized earlier than patients treated without augmentation. Use of Achilles tendon allograft for augmentation yielded satisfactory results in massive ruptures, such as in the case of late repair of bilateral patellar tendon rupture by Muratli et al (8).

No standard postoperative rehabilitation protocol existed in current literature, except for our previous study, which addressed rehabilitation after tibial tuberosity fractures (14). In our case, an end-to-end suture, reinforcement with a cerclage wire, and fixation with footprint anchors were used. In our opinion, combination of all three methods was suitable to address the extensive rupture of the patellar tendon and could reduce the risk of tendon re-rupture. Moreover, use of footprint anchors compared to the use of staples or K-wire fixation doesn't require reoperation for implant removal. In the follow-up of our patient, we were able to observe good functional and radiological outcomes following our approach. Informed consent was waived from the patient for inclusion in the study. All procedures in the studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethics

Informed Consent: Written informed consent was obtained from the patient and their legal guardians for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ö., A.A., Concept: H.Ö., Design: T.Ö., R.D., G.B., Supervision: H.Ö., A.A., Resources: G.B., Material: R.D., Data Collection or Processing: A.A., Literature Search: A.A., T.Ö., R.D., Writing: A.A., R.D., Critical Review: A.A., H.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Gazi Med J 2025;36(2):214-217

Özer et al. Subacute Patellar Tendon Avulsion in a Child

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Urinary Tract Cistern as a Rare Cause of Huge Abdominal Cystic Mass in an Infant: A Case Report

İnfantta Dev Abdominal Kistik Kitleye Neden Olan Nadir Bir Üriner Sistem Sarnıcı: Olgu Sunumu

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ABSTRACT

Megaureter is defined as a lower-end ureter diameter greater than 7 mm in children. Although often diagnosed antenatally, postnatal presentation can occur with urinary tract infections, abdominal pain, hematuria, or incidentally. We present a rare case of a urinary cistern, which was an ectopic ureter of an aborted left duplicated system, forming a giant abdominal mass and causing contralateral hydroureteronephrosis with bilateral undescended testes.

Keywords: Urinary tract cistern, megaureter, abdominal cystic mass, undescended testes

ÖZ

Çocuklarda megaüreter, alt uç üreter çapının 7 mm'den büyük olması olarak tanımlanır. Genellikle antenatal dönemde teşhis edilse de, postnatal olarak idrar yolu enfeksiyonları, abdominal ağrı, hematüri veya tesadüfen tespit edilebilir. Bu olguda, sol duplike sistemin gelişememiş ektopik üreteri olduğu düşünülen ve dev bir abdominal kitle oluşturan nadir bir üriner kist örneğini sunuyoruz. Bu kitle, karşı tarafta hidroureteronefroza ve bilateral inmemiş testislere neden olmuştur.

Anahtar Sözcükler: Üriner sistem sarnıcı, megaüreter, abdominal kistik kitle, inmemiş testis

INTRODUCTION

In children, a lower-end ureter diameter greater than 7 mm is considered megaureter (1). Apart from antenatal ultrasound, postnatal diagnosis can be made after admission with urinary tract infection, abdominal pain, hematuria, uremia, or incidentally (2). We present a case of a urinary cistern, considered to be the left ectopic ureter of an aborted left duplicated system, which was so enlarged that it formed a giant palpable mass in the abdomen, causing hydroureteronephrosis of the contralateral right kidney and bilateral undescended testes.

CASE REPORT

A 1-year-old male patient was referred to our outpatient clinic due to a palpable mass in the abdomen. Antenatal ultrasonography done elsewhere, revealed atrophic left kidney and hydronephrosis of the right kidney. The pediatrician started antibiotic prophylaxis

for the patient after having a urinary tract infection. On physical examination, a mobile and painless firm mass of approximately 10 cm was palpated inferior to the umbilicus (Figure 1). Both the patient's testicles were nonpalpable, and the scrotum was hypoplastic. The laboratory evaluation was normal, while the radiological imaging revealed left atrophic kidney, and moderate right hydronephrosis. The cystic mass was thought to be associated with the left urinary tract, producing a urinary cistern, which was later identified as the left ectopic ureter of an aborted left duplicated system entering the urethra posterolaterally during surgery (Figure 2). The bladder was pushed to the right by a 10 cm lower abdominal cystic mass extending to the midline and superiorly from the umbilicus; and the diameter of the lower end of the right ureter was reported as 14 mm. Bilateral testes were not observed in the scrotal sac in ultrasonography. During voiding cystourethrography, the patient could be catheterized with difficulty, as the bladder was pushed to the right by the mass, whose capacity was small. There was

Gazi Med J 2025;36(2):218-220

Bulut et al. Urinary Tract Cistern as a Rare Cause of Huge Abdominal Cystic Mass in an Infant

no vesicoureteral reflux. Dimercaptosuccinic acid static kidney scintigraphy showed differential function of 98% for the right kidney and 2% for the left.

After cystoscopy and urethral catheterization, it was decided that the patient would undergo abdominal exploration. In cystoscopy, the anterior urethra was normal, but the bladder could not be entered from the posterior urethra because the bladder neck was lifted and angulated by the mass. Using a midline vertical incision in the supine position, the mass that filled the abdomen was exposed; the superior part was deperitonealized. It was removed en bloc by separating it from the bladder, the left ureter with drainage of the atrophic kidney, the posterior urethra, and the rectum, which was attached inferiorly and posteriorly by sharp-blunt dissection. Due to the thinning of the posterior bladder wall, an 8 Fr cystostomy catheter was left in the bladder. Then, a left nephroureterectomy was performed for the atrophic kidney and ureter. Both testicles were located intraperitoneally, and bilateral vasa deferentia were absent. The right testicle was severely hypoplastic; thus, the left

Figure 1. A mobile and painless giant abdominal mass

Figure 2. Schematic drawing of the intraoperative findings

orchidopexy and right orchiectomy were performed. The patient's mass pathology was reported as a benign cystic lesion that may have arisen from unregressed embryogenic residue.

DISCUSSION

Very few cases have been reported, as is the case with the giant ureter in a duplex system that presented as an abdominal mass in neonate (3). When all the cases were considered in the limited literature, fetal abdominal cysts may be associated with chromosomal abnormalities. In these cases, chromosome analysis must be performed (4). Our patient's karyotype analysis resulted as normal. Antenatal ultrasonography is critical in the diagnosis of abdominal cystic masses (5). Although detecting an apparent fetal abdominal cyst with ultrasonography is straightforward, identifying its true origin can be problematic. However, fetal abdominal cysts can be derived from different systems (such as hepatobiliary and genitourinary tracts); thus, the prognoses of masses with different origins vary greatly (6). Therefore, accurate prenatal diagnosis can provide valuable information for clinicians. The differential diagnosis of cystic lesions in the fetal abdomen includes hepatobiliary cysts such as choledochal cysts and cystic biliary atresia, renal and adrenal cysts, gastrointestinal cysts such as intestinal dilatations and duplications, ovarian cysts, ureteroceles, dilated ureter. It is very important in such cases to rule out other common pathologies, such as an ovarian cyst or other pelvic cystic masses, both of which can present similarly and show bilateral hydroureteronephrosis (7). Radiological imaging and anatomical dissection are important aids in the differential diagnosis. Hepatobiliary cysts are proximal to and associated with the liver, while intestinal cysts and duplications involve the mesentery. Ovarian cysts are a possibility in the female fetus. Male genital anomalies such as undescended testicles and absence of vas deferens may also be observed accompanying cystic masses, as in our case (8).

In this case, the cystic mass was considered to be associated with the left urinary tract, producing a urinary cistern. This cistern was later considered to be the left ectopic ureter of an aborted left duplicated system, entering the urethra posterolaterally during surgery. Left nephroureterectomy was performed for the atrophic kidney and ureter. In addition, preserving the compressed contralateral ureter of the solitary functioning kidney during dissection during nephroureterectomy is an important technical point that should always be kept in mind (9).

CONCLUSION

The pathogenesis of primary megaureter remains unclear and may involve embryological remnants. Cystic masses and urologic cysts can may be associated with megaureter and duplicated systems. In infants with abdominal masses, consider rare causes such as urologic cisterns related to ectopic ureters, aborted duplications, or embryological remnants. Radiological imaging is crucial for differential diagnosis.

Ethics

Informed Consent: It was obtained.
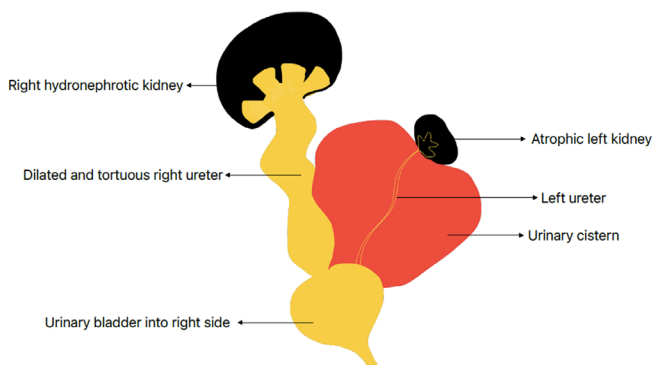
Gazi Med J 2025;36(2):218-220

Bulut et al. Urinary Tract Cistern as a Rare Cause of Huge Abdominal Cystic Mass in an Infant

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ö.T., S.G., Concept: E.C.B., N.K., M.Ö.T., S.G., Design: N.K., Supervision: M.Ö.T., S.G., Resources: N.K., M.Ö.T., Material: S.G., Data Collection or Processing: E.C.B., N.K., Analysis or Interpretation: E.C.B., M.Ö.T., Literature Search: N.K., Writing: E.C.B., N.K., M.Ö.T., Critical Review: M.Ö.T., S.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Is Laparoscopic Distal Gastrectomy A Justified Approach for Adult Hypertrophic Pyloric Stenosis, a Rare Cause of Gastric Outlet Obstruction? (with video)

Nadir Bir Mide Çıkış Obstrüksiyonu Nedeni Olan Erişkin Hipertrofik Pilor Stenozunda Laparoskopik Distal Gastrektomi Yaklaşımı Uygun Bir Tedavi Seçeneği Midir? (video ile)

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ABSTRACT

Idiopathic hypertrophic pyloric stenosis (IHPS), which affects 0.2% to 0.4% of children, is caused by the hypertrophy of the pylorus muscle layer. This condition leads to stenosis and non-bilious vomiting. Adult IHPS (AIHPS) is rare and typically occurs in males aged 30-60 years. This report discusses the case of a 39-year-old male diagnosed with IHPS following surgery. The patient, who complained of abdominal swelling, nausea, and vomiting, was diagnosed with gastric outlet obstruction on computed tomography (CT) and upper gastrointestinal endoscopy (UGE). Laparoscopic distal gastrectomy with Roux-en-Y reconstruction was performed due to unsuccessful endoscopic intervention and ongoing symptoms. The pathological diagnosis was consistent with that of IHPS. Laparoscopic distal gastrectomy with Roux-en-Y reconstruction is an effective treatment for AIHPS. It minimizes discomfort, reduces hospital stay and recovery time, and provides definitive diagnoses with minimal invasiveness. Laparoscopic skills are crucial. Further research and extended follow-up are required to confirm standard care for AIHPS.

Keywords: Gastric outlet obstruction, adult idiopathic hypertrophic pyloric stenosis, laparoscopic distal gastrectomy, Roux-en-Y reconstruction

ÖZ

İdiyopatik hipertrofik pilor stenozu (IHPS), çocukların %0,2 ila %0,4'ünü etkileyen ve pilorun muskular tabakasının hipertrofisinden kaynaklanan bir hastalıktır. Bu durum stenoza ve safrasız kusmaya neden olur. Erişkin idiyopatik hipertrofik pilor stenozu (AIHPS) ise nadir görülen ve genellikle 30-60 yaş arası erkekleri etkileyen bir rahatsızlıktır. Bu takdimde, ameliyat sonrası IHPS tanısı alan 39 yaşındaki bir erkek hasta ele alınmaktadır. Karın şişkinliği, bulantı ve kusma şikayetleriyle başvuran hastaya, bilgisayarlı tomografi ve üst gastrointestinal endoskopi sonucunda gastrik çıkış obstrüksiyonu tanısı konuldu. Endoskopik müdahalenin başarısız olması ve semptomların devam etmesi üzerine laparoskopik distal gastrektomi ve Roux-en-Y rekonstrüksiyonu uygulandı. Patolojik tanı IHPS ile uyumluydu. AIHPS tedavisinde Roux-en-Y rekonstrüksiyonlu laparoskopik distal gastrektomi etkili bir yöntemdir. Bu yöntem hasta rahatsızlığını, hastanede kalış süresini ve iyileşme süresini minimize eder, ayrıca minimal invaziv şekilde kesin tanı sağlar. Bu prosedürde laparoskopik beceriler kritik önem taşır. AIHPS için standart tedavi protokolünün doğrulanması amacıyla daha kapsamlı araştırma ve uzun süreli takip gerekmektedir.

Anahtar Sözcükler: Mide çıkış obstrüksiyonu, erişkin idiyopatik hipertrofik pilor stenozu, laparoskopik distal gastrektomi, Roux-en-Y rekonstrüksiyon

Gazi Med J 2025;36(2):221-225

Türkoğlu et al. Laparoscopic Distal Gastrectomy for Adult Hypertrophic Pyloric Stenosis

INTRODUCTION

Idiopathic hypertrophic pyloric stenosis (IHPS) affects children at an incidence of 0.2% to 0.4% (1). IHPS is caused by hypertrophy of the muscle layer of the pylorus, leading to stenosis. This condition is characterized by vomiting of non-bilious gastric contents and partial gastric outlet obstruction. There is no congenital component to it. Adult-type IHPS (AIHPS) is extremely rare; most physicians are unaware of it. Most patients with AIHPS present with symptoms and signs between the ages of 30 and 60 years (2). Males are three times more likely to experience this condition than females (2). In this case report, we discuss a 39-year-old male patient who was diagnosed with IHPS stenosis postoperatively.

CASE REPORT

A 39-year-old male patient was recently admitted to our emergency department complaining of abdominal swelling, nausea, and vomiting. The patient also experienced weight loss of approximately 6 kg in the previous few months. Upon admission, an upright abdominal radiograph revealed a nonspecific small-bowel gas pattern in the upper right and lower quadrants (Figure 1). Laboratory results showed elevated blood urea nitrogen levels at 48 mg/dL; creatinine levels at 2.43 mg/dL; low serum potassium at 2.6 mEq/L; low chloride at 69 mEq/L; and a high pH of 7.57. These findings indicated hypokalemic-hypochloremic metabolic alkalosis and the development of acute renal failure. Following these diagnoses, the patient was hospitalized at a nephrology clinic for further evaluation and treatment. A multidetector CT was performed upon renal function restoration, revealing only gastric distension with no masses or lymphadenopathy (Figure 2). UGE revealed a distended stomach with food residue and stenotic pylorus (Figure 3). Despite nasogastric decompression and fluid resuscitation, a subsequent UGE intended for pyloric sphincter dilation failed, as the scope could not pass through the stenotic pylorus. The patient whose symptoms did not improve was referred to our clinic. The patient, who had no other known health issues, had experienced occasional bouts of nausea and vomiting over the past decade, typically involving the patient's ingested food. Since we could not rule out gastric malignancy from the differential diagnosis, we planned distal gastrectomy.

Surgical Procedure

The procedure is also shown in detail in the video. The patient was positioned supine with their legs apart in the reverse Trendelenburg position under general anesthesia. Subsequently, the Veress needle was inserted. The abdomen was then inflated with CO_2 gas until a pressure of 12 cm H_2O was attained. A 30-degree camera was inserted through the 10 mm umbilical port. Under laparoscopic visualization, a 12 mm trocar was inserted 1 cm above the umbilicus along the left midclavicular line, serving as the operator's primary manipulation port. A 5 mm trocar was inserted at a symmetric location on the right side to serve as the operator-assisted manipulation port. A 5 mm trocar was inserted 2 cm below the subcostal margin at the left anterior axillary line to serve as the manipulation port for the first assistant. A Nathanson liver retractor was inserted through the subxiphoid area to elevate the left lateral segment of the liver (Figure 4).

The gastrocolic ligament was divided 3 cm away from the gastroepiploic vessels using a laparoscopic harmonic scalpel.

Specific branches of the left gastroepiploic artery and the short gastric artery were cut along the greater curvature of the stomach at a predetermined level for the division of the stomach. The lymph nodes around the origin of the right gastroepiploic vein and artery were dissected en bloc. Then, the vessels were divided at their origins. The duodenum was transected immediately distal to the pylorus using a 60 mm Endo-GIA stapler. The stomach was transected at a designated level using an endoscopic stapler.

The jejunum was grasped and transected using an Endo-GIA stapler, 20-25 cm away from the ligament of Treitz, and then marked with purple dye. The Roux-limb side of the jejunum was followed distally at a distance of 50 cm. With a harmonic scalpel, small enterotomies were performed on the antimesenteric side of the proximal loop of the jejunum and the Roux limb's distal segment to place the endoscopic stapler's fork. The stapler was introduced through the 12-mm trocar on the left abdomen. A side-to-side jejunojejunostomy was conducted using a 60-mm Endo-GIA stapler. The common entry hole was closed with intracorporeal running sutures.

The proximal segment of the Roux limb was carefully mobilized while preserving the mesenteric arch. The tension-free jejunal loop was then moved via an antecolic route. Small incisions were made at the end of the transected site of the antimesenteric surface of the Roux limb, and greater curvature of the remnant stomach. An isoperistaltic gastrojejunostomy was performed, creating a side-to-side anastomosis using an endoscopic stapler. The common entry hole for gastrojejunostomy was approached, suspended with Lambert sutures, and closed using a 60 mm endoscopic stapler. The dissected stomach was extracted through an extended umbilical incision measuring approximately 4 cm. Finally, a flat drainage tube was positioned close to the duodenal stump and behind the anastomotic site.

The patient began a clear liquid diet, gradually progressing to a regular diet on the third postoperative day. The drain was removed
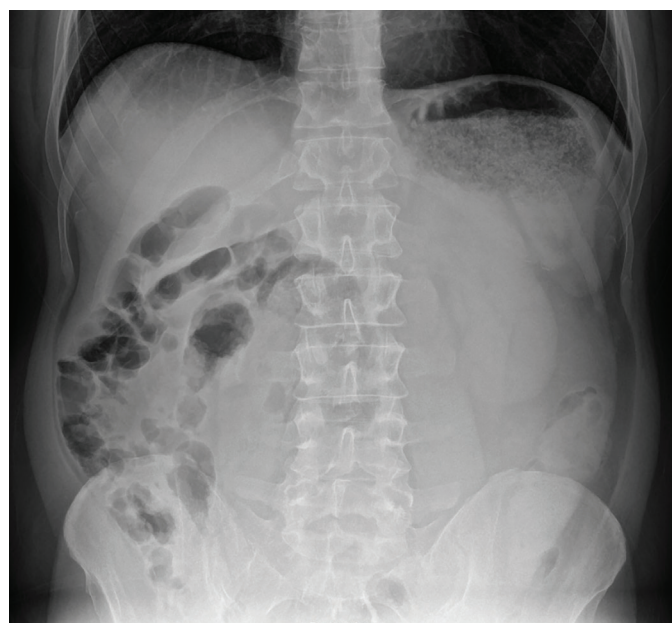

Figure 1. The upright abdominal radiograph reveals a nonspecific gas pattern in the small bowel in the upper right and lower quadrants

Gazi Med J 2025;36(2):221-225

Türkoğlu et al. Laparoscopic Distal Gastrectomy for Adult Hypertrophic Pyloric Stenosis
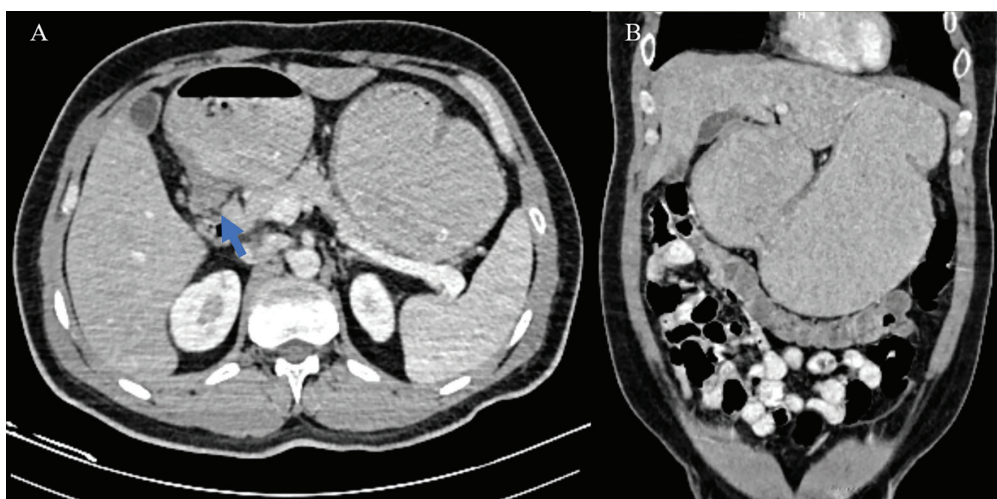
Figure 2. A. The abdominal CT scan shows a thickened distal gastric antrum and a narrowed pylorus (indicated by the blue arrow). B. The coronal view of the abdominal CT scan shows marked gastric distension
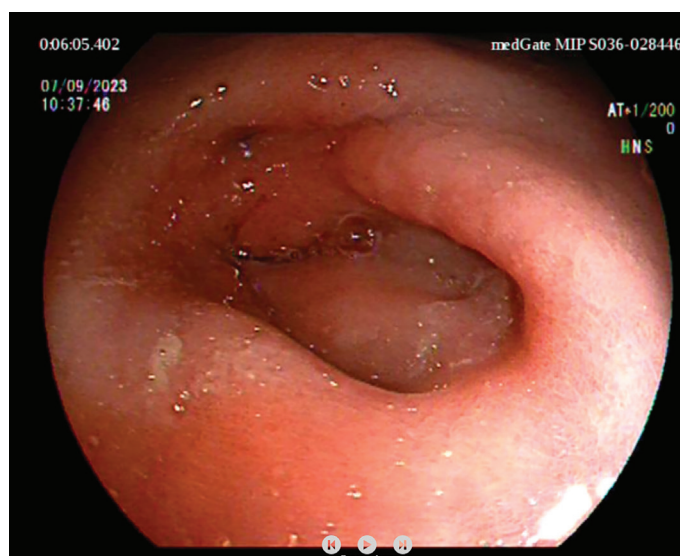
CT: Computed tomography

Figure 3. During an upper gastrointestinal endoscopy, the stenotic pylorus is visible
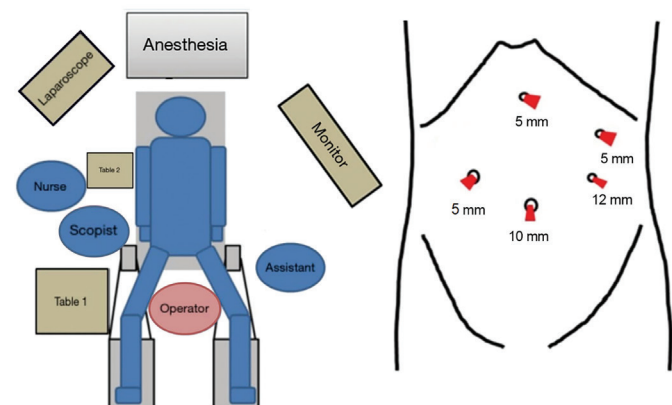

Figure 4. Positions of the operator, surgical equipment, and trocar sites for laparoscopic distal gastrectomy

on the sixth postoperative day, and the patient was discharged without complications. Pathological examination revealed that the distal gastrectomy material was characterized by increased pyloric muscle thickness and hypertrophy of the muscularis propria layer (Figure 5). The removed lymph nodes were also reactive.

DISCUSSION

AIHPS is a rare disease often underreported due to diagnostic challenges. It is most frequently reported in middle-aged men, as exemplified by our case (3). Hypertrophic pyloric stenosis (HPS) is classified into three types: type 1 HPS, diagnosed at a late stage in infants; type 2, the most common type, is occurring in adults and is often secondary to underlying gastrointestinal pathologies such as peptic ulcer disease, malignancy, and certain inflammatory diseases; and type 3, idiopathic HPS, is occurring in adults (4). Zarineh et al. (5) further divide it into primary (no underlying cause) and secondary (due to disorders like ulcers, malignancies, adhesions, bezoars, and increased vagal activity). Unlike Primary HPS, which shows muscle hypertrophy, the secondary type exhibits mild or no hypertrophy, with fibrous tissues replacing muscle fibers.

Diagnosis is based on medical history, clinical and radiological evidence, and endoscopic appearance. However, pathologists typically make the diagnoses. Patients mainly experience post-meal abdominal distension, relieved by vomiting. These symptoms include nausea and minimal pain. Symptoms, such as anorexia and early satiety, can also occur. Weight loss is a common experience among all patients. The absence of pain at symptom onset is a key diagnostic indicator. The duration of the symptoms varies from 5 weeks to 16 years (4). Our patient's intermittent symptoms of bloating, nausea, and vomiting for ten years align with the clinical findings of AIHPS.

Specific radiological findings may indicate AIHPS. A convex indentation at the base of the duodenal bulb, known as Kirklin's sign, indicates AIHPS (6,7). The "string sign" refers to an eccentric or concentric narrowing of the pyloric region (8). However, diagnosing AIHPS through imaging can be challenging because some cases
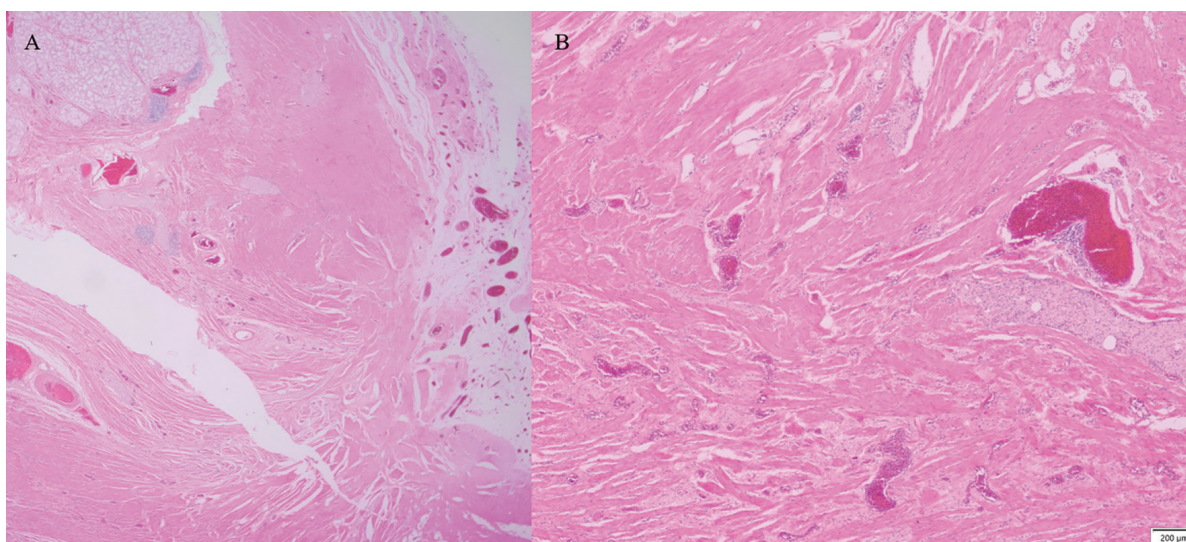
Gazi Med J 2025;36(2):221-225

Türkoğlu et al. Laparoscopic Distal Gastrectomy for Adult Hypertrophic Pyloric Stenosis

Figure 5. A. Increased thickness of the muscularis propria layer in the gastroduodenal junction (H&E x12,5) B. Hypertrophic muscle fibers in the muscularis propria layer (H&E x100)

may show average results with no distinctive signs. Abdominal CT scans help rule out secondary causes of HPS, such as malignancy. Additionally, thickening of the distal gastric wall can be identified as a unique, though nonspecific, sign of IHPS, as demonstrated in our case. Endoscopically, the pylorus is fixed, significantly narrowed, and has a smooth border. Its appearance is often described as the "cervix sign". Although peristaltic waves appear to result in some contractions, the pylorus fails to close entirely in the pyloric area. In our patient, the endoscopic observation of the "cervix sign" further validates the diagnosis of AIHPS.

Various treatments for AIHPS have been suggested, including endoscopic dilation, gastrectomy, gastrojejunostomy, pyloromyotomy, and pyloroplasty (4,9). Surgical exploration is recommended for the diagnosis and treatment of AIHPS. Full-thickness biopsy is often proposed to rule out malignancy. Most studies advocate subtotal distal gastric resection (4). Laparoscopic pyloroplasty is less invasive, but technically challenging with a thickened pylorus, typically reserved for patients in a debilitated condition (10). Despite high recurrence, endoscopic dilation is an option for high-risk patients (7). No current evidence favors one technique over another. Our patient underwent laparoscopic distal gastrectomy with Roux-en-Y reconstruction due to the consideration of malignancy in the differential diagnosis, in addition to pyloric stenosis secondary to a peptic ulcer as suggested in the literature.

Several factors led us to the decision of performing vagotomy. First, vagotomy, typically combined with other stomach procedures such as drainage, resection, or diversion, is commonly used in the management of complicated peptic ulcer disease. However, vagotomy might exacerbate gastroparesis in a chronically obstructed stomach. Therefore, the patient may be at risk of delayed gastric emptying. Second, the right vagus nerve typically appears as a single structure crossing the crura and deviating from the posterior surface of the esophagus. Conversely, laparoscopic identification of the left vagus nerve is more challenging. It often splits into smaller branches once it reaches the abdomen (11). Finally, vagotomy is less

frequent today due to the application of postoperative proton pump inhibitors (PPIs) to reduce acid secretion. Furthermore, the success of primary procedures, rather than vagotomy, mainly determines patient outcomes after peptic ulcer surgery (12).

CONSLUSION

In conclusion, laparoscopic distal gastrectomy with Roux-en-Y reconstruction is not only technically feasible but also a safe operation for AIHPS. It provides definitive diagnoses with minimal invasiveness. Also, this minimally invasive surgical technique offers patients benefits, such as decreased pain, shorter hospital stays, and reduced postoperative disability. Nevertheless, proficient laparoscopic techniques are vital for successful implementation. Additional studies and prolonged follow-up are necessary to establish a clear standard of care for patients with AIHPS.

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Challenges and Strategies for Educating Medical Students During the COVID-19 Pandemic: A Systematic Review

COVID-19 Pandemisi Sırasında Tıp Öğrencilerini Eğitmenin Zorlukları ve Stratejileri: Sistematik Bir İnceleme

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ABSTRACT

During the coronavirus disease-2019 (COVID-19) pandemic, medical student education faced many challenges as these students became involved in the treatment of disease. Therefore, the purpose of this study was to systematically review the challenges and strategies for medical student education during the COVID-19 pandemic. This study is a systematic review. To find the necessary documents and collect the information, Web of Science, PubMed, Scopus, and Embase databases, websites for relevant journals, and search engines such as Google Scholar, were used from January 2019 to the end of 2022. The data were analyzed using content analysis and descriptive statistics. Of the 14,474 studies found, 82 documents were ultimately included. Most studies were conducted in the United States (18%), and the largest target population was U.S. residents (41%). A total of 228 challenges were identified and categorized into seven major themes (financial constraints and infrastructure development, international education, assessment and testing system, student health and preparation, professional ethics, faculty empowerment, and virtual education) and 14 subthemes. The most significant challenges were virtual education, student health, and financial and infrastructure constraints. Solutions were also categorized into five main areas: virtual education, infrastructure and physical environment, educational approach, faculty empowerment, and health, along with 23 subcategories. Identifying

ÖZ

Koronavirüs hastalığı- 2019 (COVID-19) pandemisi sırasında, tıp öğrencilerinin eğitimi, bu öğrencilerin hastalığın tedavisine dahil olmalarıyla birçok zorlukla karşılaştı. Bu nedenle, bu çalışmanın amacı, COVID-19 pandemisi sırasında tıp öğrencisi eğitimiyle ilgili zorlukları ve stratejileri sistematik bir şekilde incelemektir. Bu çalışma bir sistematik derlemedir. Gerekli belgeleri bulmak ve bilgileri toplamak için Web of Science, PubMed, Scopus ve Embase veritabanları, ilgili dergilere ait web siteleri ve Google Scholar gibi arama motorları kullanılarak Ocak 2019'dan 2022 yılı sonuna kadar olan dönemde araştırma yapılmıştır. Veriler içerik analizi ve tanımlayıcı istatistikler kullanılarak analiz edilmiştir. Toplamda 14.474 çalışma bulunmuş olup, bunlardan 82 belge nihai olarak dahil edilmiştir. Çalışmaların çoğu Amerika Birleşik Devletleri'nde (%18) yapılmış olup, en büyük hedef kitle ABD vatandaşlarından (%41) oluşmuştur. İki yüz yirmi sekiz zorluk belirlenmiş ve yedi ana tema (finansal kısıtlamalar ve altyapı geliştirme, uluslararası eğitim, değerlendirme ve sınav sistemi, öğrenci sağlığı ve hazırlık, profesyonel etik, fakülte güçlendirme ve sanal eğitim) ve 14 alt tema altında kategorize edilmiştir. En önemli zorluklar sanal eğitim, öğrenci sağlığı ve finansal ve altyapı kısıtlamaları olarak belirlenmiştir. Çözümler de beş ana alan altında kategorize edilmiştir: sanal eğitim, altyapı ve fiziksel çevre, eğitim yaklaşımı, fakülte güçlendirme ve sağlık, ayrıca 23 alt kategori bulunmaktadır. Bu çalışmada sunulan

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

ABSTRACT

and analyzing the challenges presented in this study and the solutions offered could help policymakers and higher education managers make evidence-based decisions tailored to local conditions, and turn the COVID-19 crisis into an educational opportunity.

Keywords: COVID-19, education, students, medical sciences, challenge, solutions

ÖZ

zorlukların ve önerilen çözümlerin belirlenmesi ve analiz edilmesi, politika yapıcıların ve yükseköğretim yöneticilerinin yerel koşullara göre özelleştirilmiş kanıta dayalı kararlar almalarına yardımcı olabilir ve COVID-19 krizini bir eğitim fırsatına dönüştürebilir.

Anahtar Sözcükler: COVID-19, eğitim, öğrenciler, tıp bilimleri, zorluk, çözümler

INTRODUCTION

In late 2019, the outbreak of a new virus, namely "Coronavirus Disease 2019" (COVID-19), that caused lung infections was reported in China. The disease spread rapidly, infecting over 100 million people and affecting world health. The World Health Organization announced COVID-19 as a pandemic on March 11, 2020 (1,2). Although various organizations worldwide have taken numerous measures to respond to this crisis, people's lives worldwide have been disrupted, and many jobs and activities have been suspended. One of the critical areas upon which the fate and future of societies usually depend is the education system; in which the presentation process has changed with the coronavirus outbreak. In this regard, higher education systems worldwide have been compelled to provide online education. While the conditions have been difficult, they have inspired innovation to provide instruction in new ways. In other words, education at all levels has been dramatically affected, and residents, students, and medical educators are experiencing new conditions (3). Given that gathering in enclosed places such as a classroom causes the spread of the virus, classes have been closed, and dormitory and university welfare services have been reduced as well, university rules and regulations have been changed, student costs have increased, and hundreds of millions of students at different education levels have been affected (4,5).

The COVID-19 crisis has created unique educational challenges. Educating and evaluating students has entirely changed, and all universities and educational institutions worldwide have been implementing new educational strategies, such as virtual education. Universities and institutions have been teaching through various platforms, such as online and digital platforms. In other words, new distance learning methods have replaced traditional learning methods. Due to the novelty of this strategy, there are many weaknesses, and students are experiencing specific problems (6,7). According to statistics, more than 194 countries have been forced to change their educational systems due to the outbreak of the COVID-19 pandemic (6,7). Universities have shifted their in-person classes to online classes, blended learning environments, or social media education. This has caused irregularities in the conduct of classes, virtual and online learning has led to confusion and learner dissatisfaction, creating various challenges for students and reducing the quality of education.

A complete response to this crisis seems necessary because academic progress and education of residents and students depend on it (8,9). Identifying the challenges in higher education can be very helpful in making decisions and taking supportive and managerial measures. In other words, recognizing as many challenges and opportunities as possible during the COVID-19 pandemic is of great importance for higher education and university systems. Considering that conducting any kind of research in the field of higher education is regarded as a support for it and causes education to flourish, if there is a lack of higher education research, teaching and learning will become superficial and inefficient. Thus, the present study systematically examined educational challenges and strategies for medical students during the COVID-19 pandemic.

MATERIALS AND METHODS

This study is a systematic review conducted in 6 stages in 2022: identification of the research question, relevant studies, study selection, data charting, reporting quality assessment, and analyzing data and reporting the results. In this study, the systematic review approach taken from the book "Systematic Review to Support Evidence-Based Medicine" (10) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11) were used.

Identification of The Research Question

The main research question is as follows: "based on the results of previous studies, what challenges did medical students face in terms of education during the outbreak of COVID-19, and what are the main strategies to deal with these challenges?" All studies and reports related to the education of medical students during the COVID-19 pandemic, published in prestigious scientific journals in English and Persian from 2019 to the end of 2022, dealt with the challenges and solutions in the field of education. Their full texts were available and were examined. Abstracts of the articles published in conferences, seminars, and newsletters were considered exclusion criteria. Studies published in languages other than English and Persian were also excluded.

Identification of Relevant Studies

The search strategy in the present study was developed and implemented by an experienced and knowledgeable librarian who specialized in the subject area. The required data were collected by searching the Web of Science, PubMed, Scopus, and Embase databases. The search strategy was based on the following keywords: learning, education, training, "tele education", "virtual telemedicine", "e-learning", "online learning", "mobile learning", "new learning", teaching, "higher education", problem, hinder, obstacles, challenges, barrier, approach, response, answer, reaction, actions, policy, measurement. resident, student, "post graduate". COVID, "COVID-19", coronavirus, "2019 novel coronavirus", "COVID19", "2019-novel COV", "SARS-cov-2", "SARS-CoV2", "SARSCoV2", "SARSCoV-2", "severe acute respiratory syndrome coronavirus 2", "2019-ncov", "coronavirus disease 2019", "coronavirus disease-19", "2019ncov", "SARS coronavirus 2".

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

To identify and include other published articles, in addition to searching the databases, we also manually searched some relevant journals in the field, such as Medical Education, Medical Education Online, BMC Medical Education, and the International Journal of Medical Education, as well as the Google Scholar search engine. The aforementioned keywords were also used in the Google Scholar search engine. Having excluded poorly-related articles and selected the main ones, the researchers carried out reference checks, citation checks, and reviewed gray literature to increase the assurance of identifying and reviewing the selected articles.

Study Selection

After collecting all the relevant articles, duplicate ones were excluded from the study, and two researchers performed the initial screening based on the titles and abstracts. The items that did not correspond to the study's aim were also excluded. Once the articles that did not meet the inclusion criteria were removed, the full texts of all the articles meeting the inclusion criteria were reviewed. In the next step, researchers extracted the results of the reviewed articles, and finally, the full texts were assessed in terms of eligibility. The Endnote X5 resource management software was used to organize the articles, review the titles and abstracts, and identify duplicates. The PRISMA 2020 flowchart (12) was also used to report the results of the selection and screening process.

Data Charting

The data were extracted using a researcher-made form in the Microsoft Word Office 2016 software. The data extraction was performed by two independent researchers, who were experienced and knowledgeable in data extraction, and were responsible for independently extracting the data. These investigators (E.S. and Z.Z) also independently assessed relevant full-text articles for eligibility based on the predefined criteria. Any disagreements between the investigators were resolved through discussion with the third and fourth investigators (M.H. and K.K.). The data on the influencing factors reported in each study were extracted and entered into the data extraction table. The information extracted from the studies included: bibliographic characteristics such as researcher's name, research year, and journal name; a summary of the methodology of each research; research data collection tool; the study population of each research; and the most important findings and results of each study.

Quality Appraisal

The quality of the papers was examined independently by two of the researchers using the STROBE standard checklist (strengthening the reporting of observational studies in epidemiology) designed explicitly for cross-sectional studies (13). The STROBE checklist consisted of 6 general sections under the following headings: Title and abstract, introduction, methods, results, discussion, and other information. Some areas were subdivided into different subcategories, for a total of 22 sections. The scoring was conducted based on the importance of each section for the present study. The minimum acceptable scores were set at 30 and 15, respectively. Finally, the articles that achieved a minimum score of 15 points were included in the research, and their data were reviewed. Three articles that scored less than 15 were removed at this stage.

Content-Analysis and Reporting the Results

After extracting the information using the data charting form, the extracted data were manually analyzed, summarized, and reported using the content analysis method. Content analysis is a method for identifying, analyzing, and reporting the patterns (themes) within the text and is widely used in qualitative data analysis (14-16). The data were coded by two researchers independently. The data analysis and coding steps were as follows: familiarity with the texts of articles (immersion in the results), identification and extraction of primary areas (identification and extraction of the articles more related to primary areas), placement of the articles in specified areas, reviewing and completing the results of each area using the results of the articles on the areas. Ensuring the reliability of the areas and the results extracted in each area involved reaching an agreement between the two coders through discussion and resolution of disputes. Data were reported using descriptive statistics such as percentage and frequency. Excel 2016 was also used to draw the charts.

RESULTS

In this study, 14,408 articles were retrieved from databases such as PubMed, Scopus, Web of Science, and Embase. An additional 66 studies were retrieved from other sources such as Google Scholar and specialized websites. In total, 14,474 articles were identified Finally, 74 articles were reviewed via databases, and 8 articles were reviewed via searches of other sources, resulting in a total of 82 studies. After a careful and systematic review, the required information was entered into the extraction form (Figure 1).

Most of the studies were conducted in the United States (18%), Saudi Arabia (13%), India (11%), Italy (10%), China (8.5%), Canada (6%), United Kingdom (6%) (Figure 2).

The participants in the studies included residency (41%), general medicine (23%), dentistry (10%), and pharmacology (5%) students, as well as those studying in other fields (21%) (Figure 3). Most of the studies had been conducted on residency students in surgery, urology, radiology, neurology, ophthalmology, and orthopedics.

Educational challenges during the COVID-19 pandemic were categorized into seven main themes (financing and infrastructural development, rules and regulations, international education, assessment and testing system, student health and preparedness, professional ethics, faculty empowerment, and virtual education) and 14 subthemes (Table 1).

Examining the 82 studies obtained from database searches provided us with 228 educational challenges during the COVID-19 pandemic, as shown in Figure 4, based on their frequency. Three of the most common challenges included virtual education, student health challenges, and financial and infrastructural education constraints during COVID-19.

The solutions provided for education during the COVID-19 pandemic were classified into five main areas: virtual education, infrastructural and physical, educational approach, faculty empowerment, and the health area and 23 subcategories (Figure 5).

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

Table 1. Educational challenges of medical students during the COVID-19 pandemic

Main theme	Subtheme	Challenges
Financial constraints and infrastructures	Financial	• Financial constraints on Internet access, hardware shortage (17-19)
		• Financial restrictions on buying laptops or smartphones (20-22)
	Infrastructural and physical	• Unawareness of the security of e-learning programs in terms of privacy and data protection (23,24)
		• Operating system instability and inefficient ability of online education (25-27)
		• Lack of advanced electronic systems in low-income countries (28,29) problems of fourth-generation internet connection and unstable internet connection (30,31)
		• Audio-visual problems (32)
International Education	Disruptions in the international education process	• Return of exchange students to their home countries and interruption of their educational activities (33)
Assessment and testing system	Evaluation	• Lack of objective evaluation of education (34)
		• Lack of supervision of students in online education (27)
		• Difficulties of online evaluation and problems of understanding unique dynamics of online education (35,36)
Students' health and preparedness	Mental and spiritual	• Creating stress due to the risk of transmitting COVID-19 to their families (19,25,33,37,38)
		• Increased student stress due to COVID-19 infection
		• The negative impact of the epidemics on mental health (39-41)
		• Impact on students' social life (16,17,30)
		• Negative effect on students' intellectual ability (30)
		• Negative impact on their ability and confidence to be a good doctor in the future (16,42,43)
	Interest	• Students' preference for in-person education over e-learning (44,45)
		• Dissatisfaction with online education (46-48)
		• Indifference and lack of motivation to study (49-51)
Professional ethics	Ethics in education	• Prioritizing the care of patients and vulnerable people over monitoring the education of medical students (50,52,53)
	Ethics in hospital	• Reduced interaction between hospital staff and residents (54)
		• Decreased social communications (55,56)
		• Negative effect on the quality of medical care due to lack of communication with patients (57,58)
Faculty empowerment	Specialized training	• Lack of formal training of faculty members for online assessment, such as conducting and marking online exams (35)
		• Lack of knowledge and expertise of professors in online education (59-61)
	Soft skills	• Psychological aspects of telecommunications, the language of instruction, distance learning provision, and methodological problems (62)
		• An imbalance between the life and work of female teachers working at home (35,63)
Virtual education	Planning	• No guarantee of the efficiency of online education and university lectures (27,64)
		• Problems with scheduling and over-running of seminars/lectures (32,65)
	Implementation	• Lack of specific quantitative standards for measuring the quality of educational processes in online education (27)
		• Lack of knowledge and understanding of virtual education (30)
		• Insufficient communication by educational institutions and educational leadership (33)
		• Learning limitations in the laboratory or clinical skills (66-70).
	Learning	• Lack of focus when learning due to lack of direct communication (71-73)
		• Students' negative attitude towards e-learning (74,75).
		• Harder learning in e-learning (31,76)
		• Students' unpreparedness for e-learning (77,78)
		• Lack of time management in virtual education (19,36,79)
		• Lack of technical skills required to work with electronic applications (23,80)
		• Lack of direct interaction between students (55,81)
		• Lack of direct interaction between students and instructors (82,83)
	Rules	• Lack of guidelines published by the medical and dental council for online medical education (35,84)
		• Increased delay in starting educational courses (39,85)
		• Interruption of student research activities (86)
		• Delays in the graduate programs of students (87)
		• Delays in examinations and licensing of residents (88-90).

Gazi Med J 2025;36(2):226-235

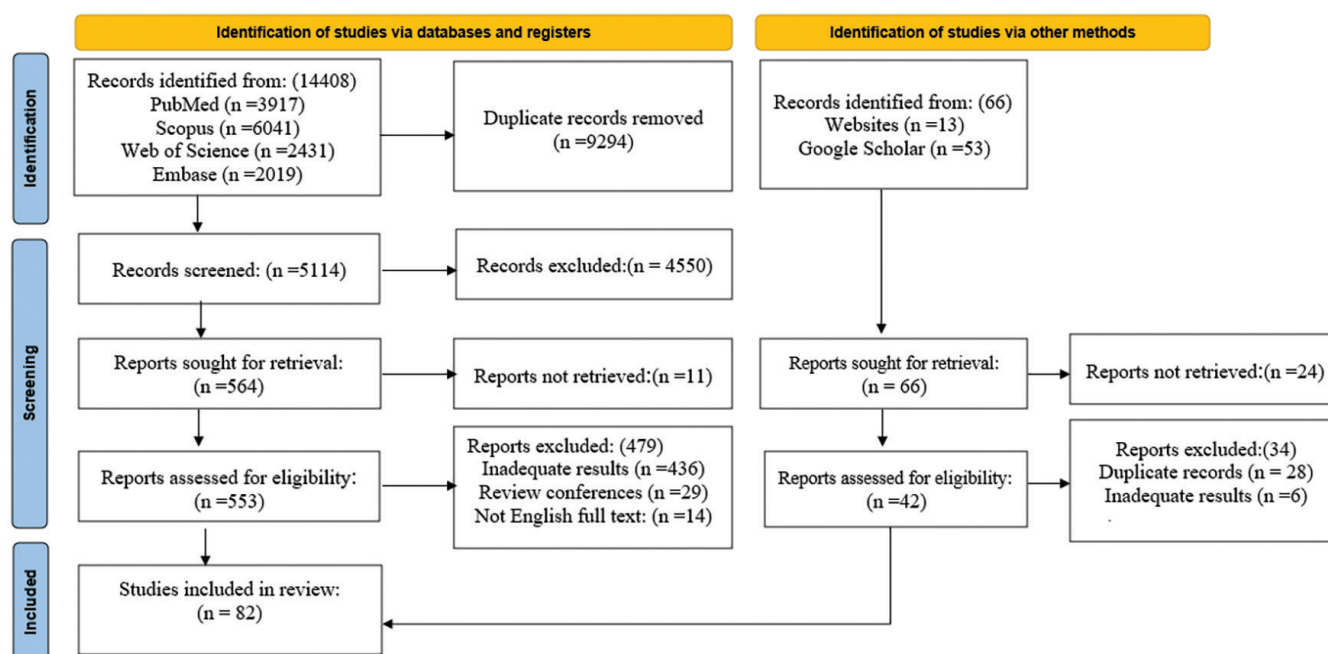Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

Figure 1. Screening process and selection of articles on challenges and strategies for educating medical students during the COVID-19 by countries

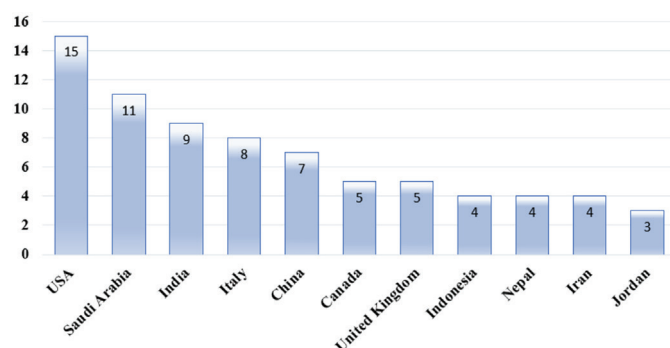*COVID 19: coronavirus disease-2019*

Figure 2. Frequency distribution of the articles on challenges and strategies for educating medical students during the COVID-19 by countries
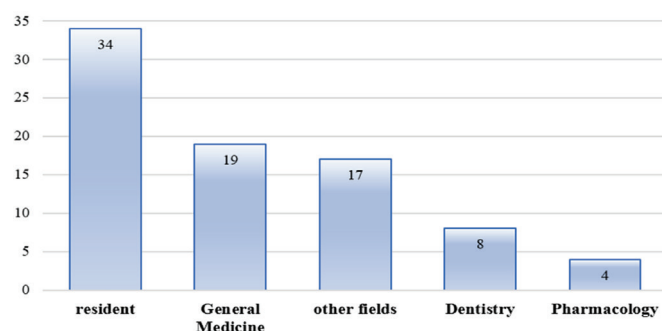
COVID 19: coronavirus disease-2019

Figure 3. Frequency distribution of the participants in the study of challenges and strategies for educating medical students during COVID-19 by discipline

COVID 19: coronavirus disease-2019

DISCUSSION

Examining the 82 studies obtained from database searches resulted in classifying educational challenges during COVID-19 into seven main themes (financial constraints and infrastructural development, international education, assessment, and testing system, student preparedness and health, professional ethics, faculty empowerment and virtual education) and 14 subthemes. The solutions provided by the studies were also categorized into five areas: virtual education, infrastructure, physical areas, educational approach, faculty empowerment, and health.

Identifying the challenges was the first step in turning them into opportunities. Most of the difficulties expressed in the studies were under the category of virtual education, and in this study, they were classified into four subcategories: planning, implementation, learning, and education rules. One of the most critical challenges in virtual education mentioned in most studies was the limitation of learning practical or clinical skills. A study conducted in Southeast Asia by Wittayanakorn et al. (91) in 2020 showed that neurosurgery residents were more concerned about a significant reduction in their surgeries, potentially leading to both a loss of existing skills and a lack of opportunities to acquire new ones. They were worried about their future because they were not confident in the assessment of their competence in neurosurgery if they were allowed to graduate from the educational course or take a national board exam (91). Development areas, such as online education modules or virtual boot camps for neurosurgery residents simulated in laboratories, enabled the students to develop practical skills (91). The current situation requires the use and promotion of these educational innovations. virtual patients (for training clinical examinations, diagnostic skills, and communication skills) virtual reality simulators (for touch training, surgical skills, and resuscitation training) have

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

shown that they can be as effective as real patients for educational purposes (29).

Other challenges of virtual education included the negative impact on the quality of medical care due to the lack of communication with patients, planning problems and over-running of seminars and lectures, and the lack of guidelines published by the medical and dental council for online medical education (32,84). Success in virtual education depends on the faculty members' attitudes and
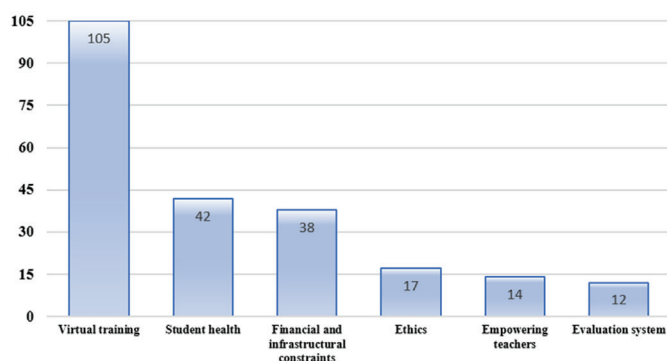
interactive teaching styles, as well as the students' experience and attitude towards technology. To increase the quality of education, choosing the appropriate method for distance education is essential. Problem-based learning approaches can ensure the understanding of important concepts and be based on critical thinking. Furthermore, faculty members can create clinical films to enhance the learning experience (92). Careful planning of online education, regular feedback in online classes, and effective time management are critical in establishing the rules of virtual education classes (18,93). Residents and other students should be encouraged to use online resources to facilitate learning. For specialist assistants, in particular, distance education through educational videos or online webinars can be integrated into academic programs. The university can positively impact students' learning through online discussions (21).

Financial and infrastructural constraints are other significant education challenges during COVID-19. Hardware and software facilities (infrastructures) play an essential role in the education system (94). According to the present study's findings, access to the fourth-generation Internet, unstable Internet connections, operating system instability, financial restrictions on access to laptops and smartphones, and lack of awareness about the security of e-learning programs could be considered infrastructural problems of virtual education. In another study, Idris and Osman. (95) attributed the

Figure 4. Frequency of the most recurring educational challenges for medical students during the COVID-19 pandemic

COVID 19: coronavirus disease-2019

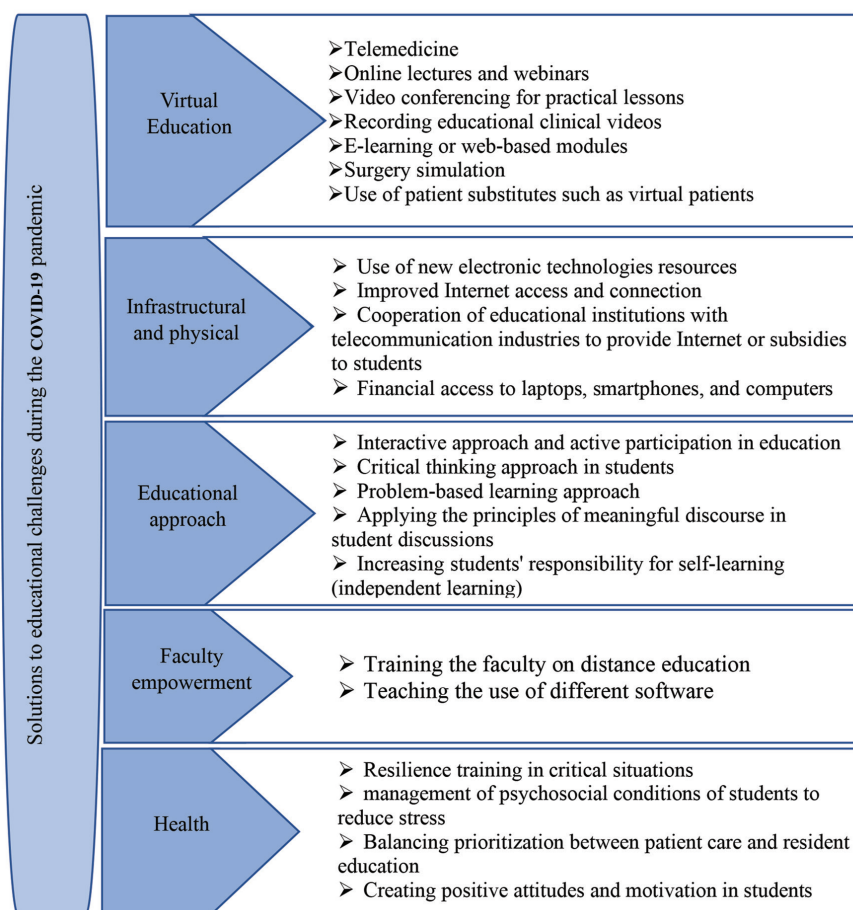**Figure 5.** Strategies to deal with educational challenges of medical students during COVID-19

COVID 19: coronavirus disease-2019

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

barriers and opportunities for implementing virtual education in Algerian universities to a lack of infrastructure, technical skills, and motivation for the staff (95). The virtual education system requires some elements, and the absence of any of these elements will lead to a severe disruption of the launch and establishment of this new system. Telecommunication and Internet infrastructures, human resource infrastructure, and experienced experts are involved in virtual education (96). Along with the constant advancement of technology and the pervasive digitalization, it is necessary to focus on the factors that facilitate e-learning. Utilizing new electronic technology resources, improving internet access and connection, cooperation between educational institutions and telecommunication industries to provide free internet or subsidies to students, and financial access to laptops, smartphones, and computers can facilitate virtual education (20,59,91).

Another educational challenge is associated with students' health. In other words, the pandemic has negatively affected their mental, physical, social, and intellectual abilities. Students are concerned about their knowledge and self-confidence in becoming good doctors in the future (42,97). This feeling has caused great stress and anxiety in medical students. A study conducted in Egypt also reported that the lack of personal protective equipment, negative concerns about the surgical profession, and financial pressures were essential factors affecting the mental health of residents (98). Studying the quality of life among orthopedic residents in South Korea showed a decrease in their satisfaction levels due to their exposure to COVID-19 stressors and their concerns about the possibility of transmitting the disease to their families (99). Such stress levels could significantly impact the resilience and strength of future physicians to cope with critical situations such as having critically ill patients and complex surgeries. Essential resilience training has broader benefits for performance improvement and can be incorporated into the students' curricula (42). It is also essential to balance the prioritization between patient care and resident education, and create positive attitudes and motivation in the students during the pandemic in order to reduce their stress (49,51).

Virtual education and online academic lectures have broken down space restrictions. Although they can effectively prevent crowds and the risk of infection, they may significantly reduce some students' learning efficiency due to poor self-awareness, instructors' lack of skills in online software, and lack of supervision for students (30,80). Investing in skilled human resource training is an important issue in the development of online education (100). Using experts to train the staff, students, and faculty members to benefit from this educational system can enhance user-system relationships and increase the efficiency of this system (86). Individual skills, as well as computer and Internet skills, are other important requirements that must be taken into account (101).

Reduced student-student and student-instructor (interactions and communications) were other challenges of online education. A sudden shift from a class full of friends and teachers to someone teaching on the screen can be a disappointing experience (18).

The restriction of students' interactions due to the epidemic has led to them feeling social isolation (17,56). According to the results of Freeman et al.'s study (102) and the review by Noori et al. (103), some disadvantages of online education were low control over education, inflexibility, and lack of face-to-face interactions. They showed adverse effects on effectiveness and learner satisfaction

(102,103). Vonderwell (104) considered the delayed feedback from the instructors and the feelings of isolation as the disadvantages of online training courses, and believed these disadvantages resulted from not communicating with the instructor (104). Students are more satisfied with interactive online sessions than with other methods, such as webinars and lectures. Thus, classes can be divided into smaller groups for better interactions (69). In addition, the focus should be on active student participation. Expression and thinking, in terms of course content creation manifested in making course contents with the students' previous experiences and knowledge, and interpretation through analysis, integration, and evaluation of one's and others' perceptions, supports students' shared knowledge and allow them to make inferences by extending their understanding and knowledge to wider areas. Therefore, critical reflection in learning can help students develop and strengthen their metacognitive skills (82). Some limitations of this study include reviewing only English language articles and focusing on higher education.

CONCLUSION

The COVID-19 pandemic posed numerous problems to all aspects of societies, including public health. Although education during this period had challenges for students, it led to the flourishing of some capabilities, such as the integration of virtual education. Based on this article, some of the specific experiences highlighted are:

Financial constraints on Internet access, hardware shortage, and lack of advanced electronic systems in low-income countries are major challenges for students trying to access online education. Lack of direct communication, interaction between students and instructors, and supervision in online education leads to difficulties in learning and evaluation, and negative attitudes towards e-learning. The COVID-19 pandemic has had a negative impact on students' mental health, social life, and intellectual ability, creating stress and interrupting educational activities. The solutions provided for education during the pandemic include virtual education through telemedicine, online lectures, webinars, video conferencing, e-learning, and simulation. Other solutions involve improving infrastructure, providing financial access to technology, and empowering faculty through training and teaching them to use different software. Health-related solutions include resilience training and management of psychosocial conditions of students. These experiences and solutions highlight the challenges and potential solutions for education during the COVID-19 pandemic and the importance of addressing issues related to infrastructure, technology, and mental health to ensure effective and accessible online education. Therefore, identifying these challenges and providing executive solutions can help higher education managers and policymakers make evidence-based decisions and turn this threat into an educational opportunity.

Ethics

Informed Consent: Our study is a systematic review, and consent information is not typically required for such studies.

Footnotes

Authorship Contributions

Concept: K.K., S.A.A., M.H., Design: K.K., M.H., Supervision: K.K., S.A.A., M.H., Resources: Z.Z, E.S.H, Material: K.K., M.H., Z.Z., E.S.H., Data

Gazi Med J 2025;36(2):226-235

Kalavani et al. Medical Education in COVID-19: Challenges and Strategies

Collection or Processing: S.A.A., Z.Z, E.S., Analysis or Interpretation: K.K., S.A.A., M.H., Literature Search: K.K., M.H., Writing: K.K., S.A.A., M.H., Z.Z, E.S., Critical Review: K.K., S.A.A., M.H., Z.Z, E.S.

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Efficacy of Apoptic Agents in Cervical Cancer Treatment

Servikal Kanser Tedavisinde Apopitotik Ajanlarin Etkinliği

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ABSTRACT

Cervical cancer is one of the prevalent gynecologic cancer in the world. Through the cancer development mechanism, it is well known that apoptosis is so important. Many of the studies investigate the relation between apoptosis and carcinogenesis and related to this treatment regimen also. In this review, we aimed to analyse new opportunities in cervical cancer treatment, in the light of the literature.

Keywords: Cervical cancer, apoptosis, targeted therapy

ÖZ

Serviks kanseri en sık görülen jinekolojik kanserlerden biridir. Kanser gelişim mekanizmasında apopitozisin önemi bilinmektedir. Birçok çalışmada apopitozisin karsinogenezle ilişkisi ve buna bağlı olarak tedavi rejimleri araştırılmaktadır. Bu derlemede; literatür ışığında servikal kanser tedavisi alanında yeni seçenekleri araştırmayı hedefledik.

Anahtar Sözcükler: Servikal kanser, apopitozis, hedeflenmiş tedavi

INTRODUCTION

Cervical cancer is the second most prevalent cancer among women and the fourth leading cause of gynecological cancer-associated deaths globally, with around 660,000 new cases and 350,000 deaths in 2022 (1). Unfortunately, in developing countries that do not have cervical cancer screening and prevention programs, cervical cancer remains the most common gynaecologic cancer (17.8 per 100,000 women), and leading cause of cancer deaths (9.8 per 100,000) among all types of cancer in women (2). Despite this being one of the most preventable and treatable forms of cancer, it is crucial that it is detected early and managed effectively. The primary goal of cervical screening is to prevent cervical cancer. This would be achieved by the detection, treatment, and follow-up of preinvasive cervical lesions (3,4)

Essentially all cervical cancers arise from persistent genital human papilloma virus (HPV) infections. It is a classic example of virus-induced carcinogenesis. Persistent sexually transmitted infection with about 15 high-risk human papilloma virus (hr-HPV) types leads to cervical cancer, with HPV-16 and HPV-18 infections accounting for about 70% of the total cases (5,6). According to the 11 case-control studies, HPV types 16, 18, 45, 31, 33, 35, 52, and 58 accounted for 95 percent of the HPV DNA-positive squamous-cell carcinomas (7).

HPV infection leads to cancer through multiple pathways, but interaction of the HPV *E6* and *E7* gene (early gene 6 and 7) products with p53 and *retinoblastoma* gene (pRb) is critical: By inactivating or activating degradation of their targets, *E6* and *E7* gene eliminate genetic surveillance and allow unchecked cell cycling, leading to the accumulation of mutations and eventual invasive cancer. Initial infection in basal epithelial cells leads to establishment of a ring chromosome from which carcinogenic proteins are elaborated while virion production occurs in maturing epithelium. Disruption of the ring, often at the HPV *E2* regulatory region, allows integration of *E6* and *E7* sequences into the host genome. The accumulation of mutations leads to nuclear changes visible cytologically as a high-grade squamous intraepithelial lesion and histologically as

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Gazi Med J 2025;36(2):236-241

İşçi Bostancı and Önen. Apoptotic Agents and Cervical Cancer Treatment

high-grade cervical intraepithelial neoplasia (CIN). Selection for invasiveness and metastasis through additional mutation and through gene methylation results in the evolution of cancer (8).

E6 increases telomerase activity in keratinocytes through increased transcription of the *telomerase catalytic subunit* gene via induction of c-myc (9,10). E6 mediation of telomerase activity may predispose individuals to long-term infection and the development of cancer (11).

The *E7* gene product is a nuclear phosphoprotein that associates with the product of the *pRb* gene (*pRb*), which is a *tumor suppressor* gene important in the negative control of cell growth (12,13). Degradation of p53 by E6 and the functional inactivation of Rb by E7 represent the main mechanisms whereby expression of HPV E6 and E7 oncoproteins subverts the function of the negative regulators of the cell cycle (14,15). Deregulated expression of the viral oncogenes is a predisposing factor for the development of HPV-associated cancers.

Apoptosis refers to programmed cell death and the "intentional" induction of cell death. Cell death is important in the growth and development of an organism because as an organism matures and differentiates, cells must die to give way to more differentiated and specialized cells (16). If the apoptosis mechanism does not work and a cell becomes immortal, it can result in tumor formation or cancer. In cancer, apoptosis appears to be a mechanism for deleting cells from the population that have sustained carcinogenic DNA damage; however, when genes such as B-cell lymphoma-2 (BCL-2) and Tp53 are involved, these cells are suddenly free to continue replicating and propagating their mutations. This genetic instability may be an early step in the development of cancers. Mutations in BCL2 and Tp53 may then influence the effectiveness of these therapies through their ability to inhibit cell death (17).

Apoptosis is a balance between proliferation and death of the cell. It is critical in mammals because it plays a role in development as well as homeostasis (18). The apoptotic pathway is activated by both intrinsic and extrinsic signals, that are referred to as the mitochondrial and death receptor pathways. The intracellular signals include DNA damage, whereas the most frequent extracellular signals are death-inducing signals produced by cytotoxic T cells from the immune system in response to damaged or infected cells (19). After the signaled apoptosis, changes begin to occur within the cell which include activation of caspases (cysteine aspartyl-specific proteases) that cleave cellular components required for normal cellular function such as cytoskeletal and nuclear proteins. As a result of caspase activity, apoptotic cells begin to undergo plasma membrane changes that signal the macrophage response (20).

The intrinsic pathway is regulated by the BCL-2 protein family that includes proapoptotic effector proteins, proapoptotic BH3-only proteins, and antiapoptotic BCL-2 proteins (21). The antiapoptotic BCL-2 proteins inhibit apoptosis by suppressing the proapoptotic BCL-2 proteins, BCL-2 associated X protein (BAX), and BCL-2 homologous antagonist killer (BAK). BH3-only proteins inhibit the antiapoptotic BCL-2 proteins (19). As a result the imbalance of the apoptosis causes wide variety of diseases.

Cancer and Apoptosis

The hallmarks of cancer are present in all cancer cells regardless of the cause or type; these include uncontrolled growth, angiogenesis, and apoptosis deficiency. The main function of apoptosis is the prevention of cancer (21). According to this approach, targeting apoptosis should maintain effectiveness for all types of cancer treatment. There are many treatment strategies that target various stages in both the intrinsic and extrinsic pathways. Two common strategies for therapeutic targeting are stimulation of proapoptotic molecules and inhibition of antiapoptotic molecules. Anyway, there is no indication of which target is most effective. As more apoptosis-inducing anticancer drugs are designed, the most effective targets will be determined (19,20).

In almost half of all human cancers, BCL-2 expression is elevated. Related to this, the great majority of the anticancer agents depend on BCL-2/BAX-dependent mechanisms to kill cancer cells. If there is a defect in this mechanism, it causes ineffectiveness of drugs. The threshold for chemotherapy or radiotherapy is raised due to apoptosis defects, which lead to resistance to those therapies (18,20).

Intrinsic Pathway of Apoptosis

It depends on mitochondria and mitochondrial proteins. Cells can also activate their apoptosis program from inside the cell, often in response to stresses such as DNA damage or developmental signals. A key protein in the intrinsic pathway is cytochrome c, a water-soluble component of the mitochondrial electron-transport chain (22). When released into the cytosol, it binds to an adaptor protein called apoptotic protease activating factor-1 (Apaf1), causing Apaf1 to oligomerize into a wheel-like heptamer called an apoptosome. Then procaspase-9 is converted into caspase-9 that activates caspases-3 and -7. The executioner caspases immediately begin to break down proteins, leading to cell death (23). The overall pathway is regulated by the proteins of the BCL-2 family, (19). This family controls the release of cytochrome c and other intermembrane mitochondrial proteins into the cytosol. Some BCL-2 family proteins are pro-apoptotic and promote apoptosis by enhancing the release, whereas others are anti-apoptotic and inhibit apoptosis by blocking the release. BAX and BAK are the main effector BCL-2 family proteins; BAK is located in the outer membrane of mitochondria, whereas BAX is in the cytosol and translocates to the mitochondria after the activation of an apoptotic signal. Their activation depends on activated pro-apoptotic BH3-only proteins.

The BH3-only proteins are the largest subclass of BCL-2 family proteins. The cell either produces or activates them in response to an apoptotic stimulus, and they are thought to promote apoptosis mainly by inhibiting anti-apoptotic BCL-2 family proteins.

Extrinsic Pathway of Apoptosis

Extracellular signals such as the tumor necrosis factor and related apoptosis-inducing ligands, fatty acid synthase ligand, as well as other death ligands that interact with cell surface receptors, can induce activation of caspases and lead to apoptosis via an extrinsic pathway (24). Initiator procaspases-8 and -10 bind to the adaptor protein, forming the death-inducing signaling complex (19,25). Executioner caspases 3, 6 and 7 are then activated and begin the cleavage of proteins and the cytoskeleton, leading to cell death (20).
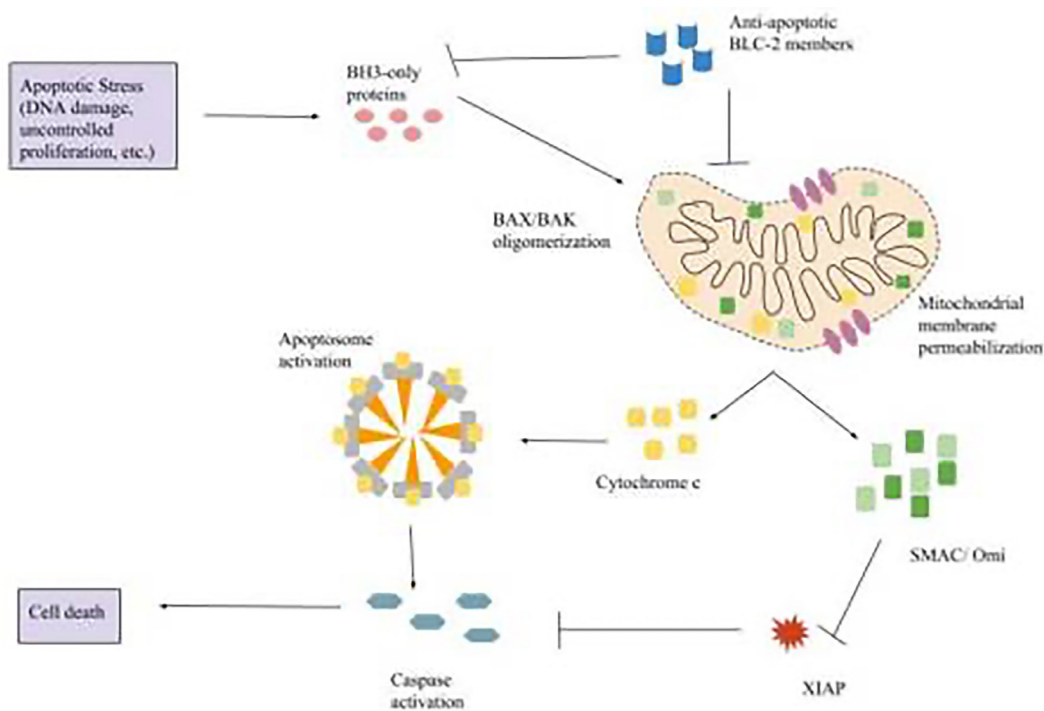
Gazi Med J 2025;36(2):236-241

İşçi Bostancı and Önen. Apoptotic Agents and Cervical Cancer Treatment

Figure 1. Intrinsic pathway of apoptosis

DNA: Deoxyribonucleic acid, BLC-2: B-cell lymphoma 2, BAX/BAK: BCL-2-associated X protein/ BCL-2 homologous antagonist/killer, SMAC: Second mitochondria-derived activator of caspases, XIAP: X-Linked Inhibitor Of Apoptosis
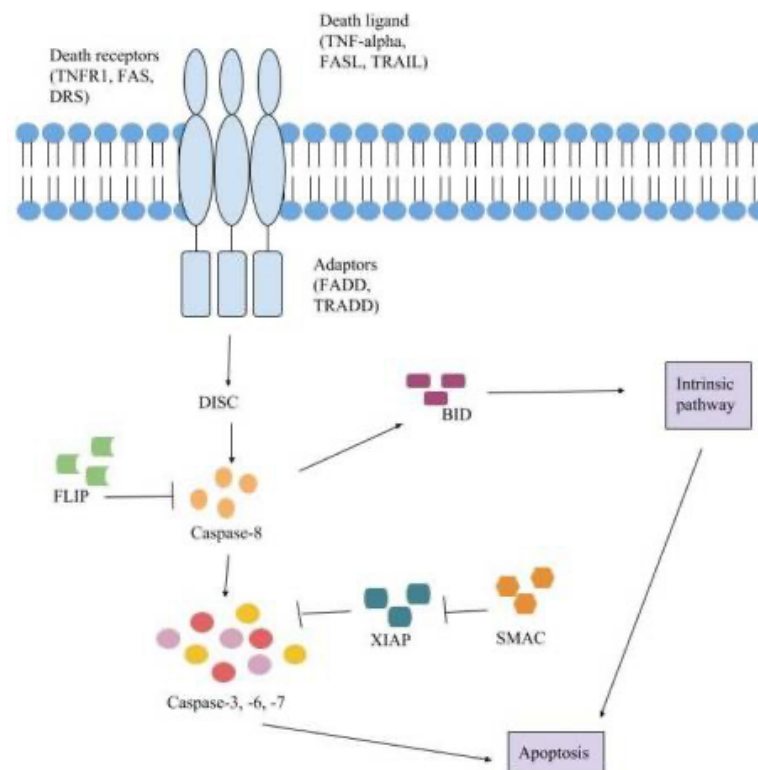

Figure 2. Extrinsic pathway of apoptosis

TNFR1: Tumor necrosis factor receptor 1, FAS: CD95L, DRS: Death receptors, TNF-alpha: Tumor necrosis factor- alpha, FASL: FAS ligand, TRAIL: TNF related apoptosis inducing ligand, FADD: Fas Associated Via Death Domain, TRADD: Tumor necrosis factor receptor type 1-associated DEATH domain protein, DISC: The death-inducing signaling complex, FLIP: FADD-like apoptosis regulator, BID: BH3 interacting-domain, SMAC: Second mitochondria-derived activator of caspases, XIAP: X-Linked Inhibitor Of Apoptosis

Gazi Med J 2025;36(2):236-241

İşçi Bostancı and Önen. Apoptotic Agents and Cervical Cancer Treatment

Cervical Cancer and Apoptosis

Current cervical cancer treatment depends on the stage of the disease and consists of surgery, radiotherapy, or chemotherapy; treatment resistance, particularly in advanced and recurrent cases of cervical cancer, remains a challenge. A deeper understanding of signaling pathways and gene aberrations in cervical cancer pathogenesis has assisted in identifying potential molecular targets for therapy and has led to the use of targeted therapies for the treatment of cervical cancer either as single agents or in combination with chemotherapeutic drugs. Thus far, bevacizumab and the immune checkpoint inhibitor pembrolizumab (which targets the PD-L1 protein) are the only targeted therapies approved by the US Food and Drug Administration for the treatment of advanced and recurrent cervical cancer. Bevacizumab is used in combination with chemotherapeutic drugs, namely cisplatin, paclitaxel, and carboplatin, to treat patients with advanced and recurrent cervical cancer. Pembrolizumab is used for the treatment of patients diagnosed with advanced recurrent cervical cancer. Approval of targeted therapies for the management of cervical cancer, has opened new treatment avenues for patients who otherwise had limited treatment options once they developed resistance to standard treatment. Targeting the BCL-2 family of proteins with BH3-mimetics for cervical cancer treatment could be a new treatment approach for cervical cancer management (26).

Relationship Between BCL-2 and EF-24

In recent years, there has been a growing tendency toward the use of phytochemicals in plants for the prevention and treatment of human diseases. Several of these phytochemicals have shown potential as cancer chemopreventive or therapeutic agents in the human body (27).

Diphenyldifluoroketone (EF-24), a monoketone analog of curcumin, is efficacious in anticancer screens and has been reported to inhibit the growth of tumor cells. It has anti-inflammatory, antimicrobial, antioxidative, immunomodulating, and anti-atherogenic features. It is suggested that EF-24 induced nuclear condensation and fragmentation , leading to the activation of caspase -3/-7, which triggers apoptosis (28). Yang et al. (27) reported that curcumin or EF-24 treatment decreased the level of BCL-2 but increased the level of BAX. The BAX/BCL-2 ratio is one of the hallmarks of the intrinsic mechanism of apoptosis in the mitochondria. So this medication helps to activate apoptosis in cancer treatment.

Effect of BCL-2 Anti-apoptotic Proteins for Cervical Cancer Progression

The expression of BCL-2 in relation to cervical cancer progression was mainly evaluated by immunohistochemistry (IHC). There were a number of studies which investigated the expression of BCL-2 in different grades of CIN (CIN, there are three CIN grades, namely CIN 1, CIN 2, and CIN 3) lesions and invasive squamous cervical carcinoma tissue sections. Using IHC, expression of BCL-2 was reported to increase with the rising grade of CIN (29,30), although, only one study showed a significant increase of BCL-2 in different CIN grades (29). Contrary to these studies, BCL-2 expression was reported to decrease with increasing grades of CIN in one study. However, there was no significant difference reported (31).

On the other hand, the five-year survival rate in cervical cancer is found positively correlated with BCL-2 expression, and it is especially associated with poor prognosis in metastatic diseases (32,33). Zhu et al. (34) also found that BCL-2-negative status was an independent predictor of pathological complete response in breast cancer patients. However, some trials had drawn different conclusions, suggesting positive BCL-2 may predict a favorable chemotherapeutic effect.

Effect of Apoptotic Proteins for Cervical Cancer Treatment

Treatment of invasive cancer involves appropriate management for both the primary lesion and potential sites of metastatic disease. In early stages (Stage I and IIA), either surgery or radiation therapy are acceptable for primary treatment, whereas chemoradiotherapy is used for advanced stages. However, there is an urgent need for more effective therapies in recurrent/metastatic cervical cancer. Clinical trials have suggested that biologic therapies may be helpful. In the literature, there are numerous studies about several agents in cancer therapies, such as angiogenic inhibitors, apoptotic agents, epidermal growth factor receptor inhibitors, mechanistic target of rapamycin pathway inhibitors, immunotherapy, monoclonal antibodies, poly(ADP-ribose) polymerase inhibitors, and more.

Especially, EF-24 acts more powerful bioactivity for anti-inflammatory and anti-cancer activity. However, the effects and mechanism of EF-24 on cervical cancer have not been fully investigated. Lee et al., evaluated the effects of EF-24 on tissue plasminogen activator (TPA)-induced cellular migration of cervical cancer. According to this article, EF-24 inhibited TPA-induced cellular migration and cellular invasion of cervical cancer cell lines by modulating MMP-9 expression via downregulating the p38 signaling pathway potential to serve as a chemopreventive agent for cervical cancer (35).

In a review, it is emphasized that targeting the apoptotic pathway is an effective option to help treat cancer, but it is necessary to systematically analyze the role of BCL-2 family proteins in regulating apoptosis and cancer treatment. Related to this, if BCL-2 and BCL-XL can be functionally blocked, the apoptosis of tumor cells can be restored. Many members of this family can be used as tumor prognostic genes and have important effects on tumor prevention and treatment (36).

Kaloni et al. (37) signed at the reduction of pro-apoptotic members of the BCL-2 family has also been implicated in the development and therapy resistance of cancer.

According to one randomised controlled trial that includes cervical carcinoma stage IIB-IIIB patients, the group treated with curcumin + radiation showed increased survival rates compared to the group treated with placebo + radiation. As a result, they have reported that curcumin is an effective, alternative radiosensitizer for application in cervical cancer treatment (38).

In addition to this, in Zhang et al. (39) study, it is noted that there is a lack of systematic reviews on the mechanism of action of curcumin against cervical cancer. Because there are few clinical trials of curcumin against cancer, and novel formulations of curcumin still need to be developed the optimal dose of curcumin for cervical cancer needs to be investigated.

Gazi Med J 2025;36(2):236-241

İşçi Bostancı and Önen. Apoptotic Agents and Cervical Cancer Treatment

CONCLUSION

Targeting the apoptotic pathway is a classic but effective approach to anticancer therapies regardless of cancer type. Because of the apoptosis deficiency, there are various mutations found in both extrinsic and intrinsic pathways in cancer. The efficacy of targeting and activating an apoptotic pathway holds promise for a significant cancer therapy. However, there is a great need to conduct further research in this field.

Footnotes

Authorship Contributions

Concept: E.İ.B., H.İ.Ö., Design: : E.İ.B., Supervision: : E.İ.B., H.İ.Ö., Resources: : E.İ.B., H.İ.Ö., Material: : E.İ.B., H.İ.Ö., Data Collection or Processing: : E.İ.B., Analysis or Interpretation: : E.İ.B., H.İ.Ö., Literature Search: : E.İ.B., H.İ.Ö., Writing: E.İ.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Gazi Med J 2025;36(2):236-241

İşçi Bostancı and Önen. Apoptotic Agents and Cervical Cancer Treatment

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Endemic Goiter in Kitâbu Divanü Lügat-it Türk: Evidence From 11th Century

Kitabu Divanü Lügatu Türk'de Endemik Guatr: 11. Yüzyıldan Bir Delil

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ABSTRACT

To present the information about endemic goiter noted in Kitâbu Divanü Lügat-it Türk (KDLT), which was overlooked in the history of medicine. The information about endemic goiter noted in the English and Turkish copies of the KDLT was reviewed in relation to goiter and thyroid hyperplasia. Further, KDLT and his author were briefly searched for using historical sources. In KDLT, which was prepared for introduction of Turkish and Turks to the Arabians in the 11th century, Mahmûd El Kashgari (1008-1102), a lexicographer of Turkic languages, noted that the "boquq" (goiter) was widespread among the Turks living in Fargana and Siqni in the Central Asia during generations. By this report, a rare source, and the first direct evidence of endemic goiter in Turks living in central Asia, has been added to the historical corpus of endemic goiter. The information related to endemic goiter in KDLT was previously not known in the medical literature, but it was in accordance with the notes of Avicenna and observations of Marco Polo, who both reported goiter in Asia in the 11th to 13th centuries.

Keywords: Goiter, thyroid gland, history of medicine, Asia, Turks

ÖZ

Bu yazının amacı, tıp tarihi çalışmalarında gözden kaçmış Kitabu Divanu Lügatu Türk (KDLT)'de bahsedilen endemik guatr bilgilerini sunmaktır. KDTL'nin Türkçe ve İngilizce tercümeleri, guatr ve tiroid hiperplazisi bağlamında gözden geçirilmiş ve ayrıca kitap ve yazarı, makalenin amacı kapsamında, kısaca, incelenmiştir. Türk dilbilimci Kaşgarlı Mahmut (1008-1102) tarafından Araplar'a Türkler'i ve Türkçe'yi tanıtmak maksadıyla 11. yüzyılda yazılan KDLT'de guatr, "bokuk/boquq" sözcüğüyle ifade edilmiş ve Orta Asya'da Fergana ve Signi bölgelerinde yaşayan Türkler'de nesiller boyunca yaygın olarak görüldüğü not edilmiştir. Bu yazıyla, ilk kez, Orta Asya'da yaşayan Türkler'de 11. yüzyıl ve öncesinde guatrın oldukça yaygın görüldüğüne dair açık bilgiler, uluslararası guatr tarihi literatürüne eklenmiştir. Uluslararası literatürde KDLT'de endemic guatr ile ilgili bilgiler olduğu daha önce hiç değinilmemiştir. KDLT'deki bilgiler, 13. yüzyılda Orta Asya'nın diğer bir kısmında yaygın guatr olduğuna dair gözlemlerden bahseden Marco Polo'nun seyahatnamesiyle ve 11. yüzyılın başlarında Asya Türk dünyasında hekim olarak çalışan İbni Sina'nın tıbbi kayıtlarıyla uyumludur.

Anahtar Sözcükler: Guatr, tiroid bezi, tıp tarihi, Asya, Türkler

INTRODUCTION

Endemic goiter has been a worldwide health problem. In Asia, medical and non-medical sources manifested its evidence starting from Chinese (29th century BC) and Hindu (21st century BC) medicine (1).

Avicenna (İbn-i Sina; 980-1037), who lived in Transoxiana (Maveraünnehir, "Çayardı") and Khurasan (Horasan) (Figure 1), mentioned swelling in the anterior neck in The Canon of Medicine (El-Kanun fi't-Tıb), which was completed in Gurgan ("Gürgan") in

1025 (2,3). However, there is no information on its incidence and the geographic area of its sufferers in the book.

The earliest information about the incidence and locations of goiters in Central Asia was presented by Marco Polo (1254-1324). During his travel in Turkestan in 1271, he noted the following sentence when he reached the province of "Karkan": "they are in general afflicted with swellings in the legs, and tumours in the throat; occasioned by the quality of the water they drink" (1,4,5). In the book about Marco Polo's itinerary written by Wright (5), it is noted that the name of

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this town could have been Yerken or Yarkund. Langer (1) also wrote that it was Yarkant ("Yarkent") County in this day and age. It is, today, a county in Xinjiang Uyghur Autonomous Region, China (Figure 1). Shaw (6) underlined that the citizens of the city spoke Turkish in the 19th century.

Another piece of non-medical evidence presenting the endemic goiter in Central Asia, back at least 100 years, is the book titled Kitâbu Divanü Lügat-it Türk (KDLT), written by Mahmûd el Kashgari (1008-1102) in 1072-1077 (7-9). This historical source of endemic goiter is not mentioned in the literature on the history of goiter available in PubMed.

KDLT is one of the earliest sources of the Turkish language and history, and it was prepared for the Arabs to introduce Turkish and Turks. It provides information about not only its definition during that period in Turkish, but also its high incidence and geographic distribution in the Turkic regions of Central Asia. The word used for goiter is "boquq/bokuk/bokok" (7-9). In Clauson's (7) English edition, "boquq/bokuk" has been described as "goitrous flesh" which grows between the skin and the flesh each side of the "Adam's apple". Mahmûd el Kashgari also noted as follows: "In Fargana and the regions of Siqni there are groups of people who are characterized by this defect. Each generation acquired these swellings anew. Sometimes they are so large that they prevent people from seeing from their own chests and feet".

This information is supported in the Union of Soviet Socialist Republics section of the World Health Organization Monograph published in 1960 (10): "The central Asiatic endemic begins at Bukhara and Samarkand and reaches its greatest intensity in the Region of Ferghana (Kirghiz), especially in the Chatkal Mountains, around the towns of Tashkent, Kokand and Andizhan", To the south of this area lies the Pamir plateau, abutting the extreme north of Pakistan, where in some valleys, notably that of the river Wanj, which flows into the headwaters of the great river Oxus (Amu-Darya), the entire population without exception is said to suffer from goitre. The endemic goiter of Ferghana and the Pamir plateau is continuous with that extending southeastward through Kashmir and the Himalayas". They also noted the connection of goitrous regions in Fergana with Yarkand in Marco Polo's itinerary (1271) as follows: "Grouped with the Ferghana focus is the endemic found throughout the mountains of Semirechensk in "The Land of the Seven Rivers" between Lake Issyk-Kul in the north of Kirghiz and Lake Balkhash in Kazakh (formerly Turkestan). It was in this part of the world that Marco Polo saw goitres when he was on his famous travels from Venice to the court of the Grand Khan in China about the year 1275. After passing through the high Pamirs, he came to the Chinese provinces of Kashgar and Yarkand at the extreme western end of the Takla Makan desert in Sinkiang (Chinese Turkestan)" (10).

In the literature, there are only a few historical texts mentioning the incidence and geography of endemic goiter (in the Alps by Pliny the Elder (AD 23/24-79); in France by Guy de Chauliac (c.1300-1368) and Valescus de Tharanta; in Italy by Arnold de Villanova (1235-1312) (1,2,4) and in some parts of Asia by Marco Polo (1271) as mentioned
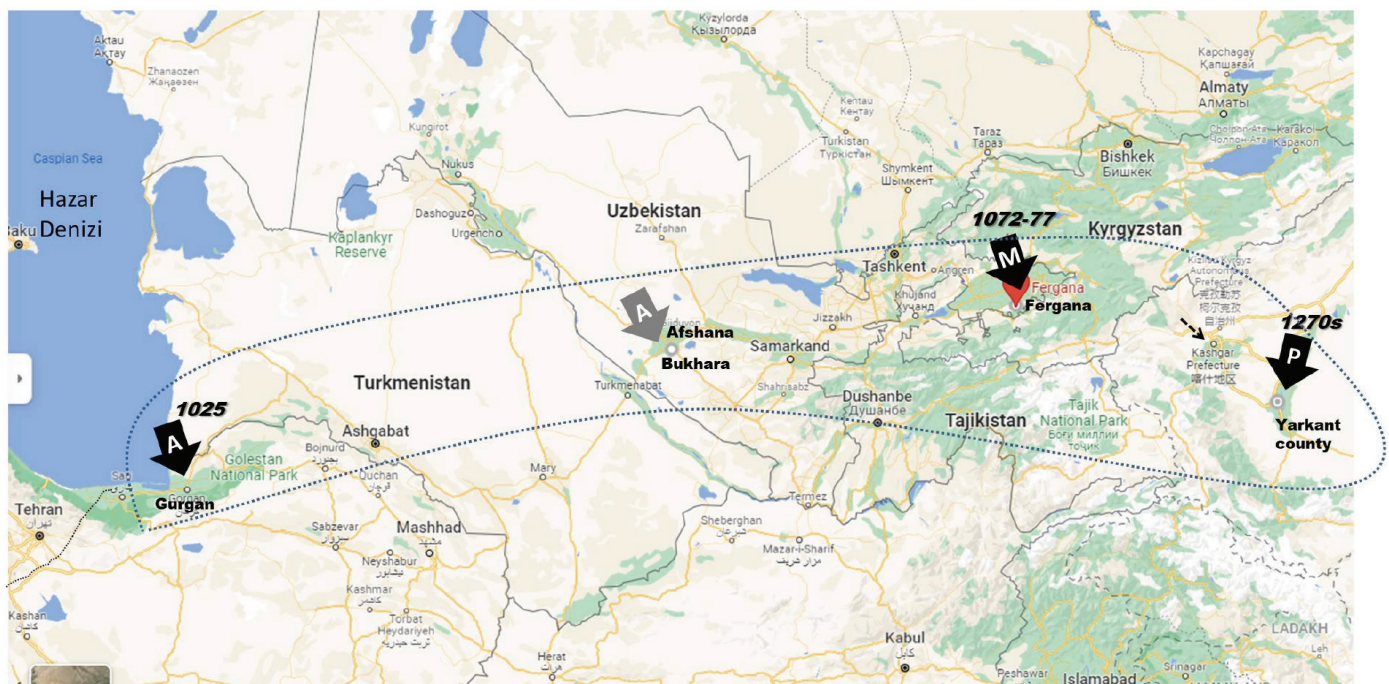

Figure 1. The Google map above presents the towns of Central Asia, which were mentioned in this paper (this map was produced in English by the Google Maps platform on November 10, 2021, and all names were kept as seen, but only the following items were added to improve readability).

"A" represents Avicenna: Afshana, next to Bukhara, is his birthplace, and Gurgan is the town where he wrote the "Canon of Medicine".

"M" represents Mahmûd el Kashgari; Fergana is the town where he mentioned the high prevalence of goiter in his work named Kitâbu Divanü Lügat-it Türk, completed between 1072 and 1077 in Baghdad. (Bagdad is out of the map.) The small dashed arrow indicates Kashgar, known as his homeland.

"P" represents Marco Polo; Yarkant ("Karkan") is the town in Turkistan where he noted a high prevalence of goiter in the 1270s, in his itinerary

above (5) Hence, it is clear that Mahmûd el Kashgari provided us a 900 years old-historical evidence for the other end of "endemic goiter belt" in the Central Asia, and this information has never been mentioned in the history of goiter as we have seen.

As we know from history, many Turks living in and around the Gurgan-Bukhara-Samarkand-Tashkent-Fergana valley-Yarkant region (Figure 1) migrated to Anatolia over the next three centuries. This migration began from the years when Mahmûd el Kashgari completed KDLT and continued until the period when Marco Polo visited Turkistan just after Avicenna lived (11,12). Unfortunately, Anatolia is also a territory characterized by iodine deficiency (13) and endemic goiter remains a significant health problem for the Turkish people living in Anatolian towns (13).

CONCLUSION

In conclusion, KDLT completes the history of the Turks with goiter from the easternmost point, Yarkent in Central Asia, to the westernmost, the West Anatolian towns in the Black Sea and inner Mediterranean regions, over more than 1000 years.

Footnotes

Authorship Contributions

Concept: Y.K.K., Design: Y.K.K., Data Collection or Processing: : Y.K.K., Analysis or Interpretation: Y.K.K., Literature Search: Y.K.K., Writing: Y.K.K.,

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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