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[1]Department of Internal Medicine Medical University Varna, Bulgaria
[2]A Clinician in the University Hospital St. Marina
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Ricardo Grillo[1,2], DDS, MBA, MSc
[1] Postgraduation Program, Departament of Oral and Maxillofacial Surgery, University of São Paulo, São Paulo-SP, Brazil
[2] Head, Departament of Oral and Maxillofacial Surgery, Faculdade Planalto Central, Brasília-DF, Brazil
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Google Scholar: HvoLLScAAAAJ&hl
ORCID ID: 0000-0001-6426-1232
ResearchGate: Ali Nasimi

Victor Nedzvetsky, PhD
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Researcher ID: V-3132-2017
Scopus Author ID: 6603483131
ORCID ID: 0000-0001-7352-441X
ResearchGate: Victor Nedzvetsky

Raphael Olszewski[1,2], DDS, MD, PhD, DrSc
[1]Department of Oral and Maxillofacial Surgery, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

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Google Scholar: 0GFkXlYAAAAJ&
ORCID ID: 0000-0002-9567-4176
ResearchGate: Ayşe Aysima Özçelik

Harry Pantazopoulos[1,2], PhD
[1]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, United States
[2]Graduate Program in Neuroscience, University of Mississippi Medical Center, Jackson, MS, United States
Researcher ID: M-1435-2016
Google Scholar: YxcCfWsAAAAJ
ORCID ID: 0000-0002-8905-8377
ResearchGate: Harry Pantazopoulos

Maria Piagkou, DDS, MD, MSc, PhD
Department of Anatomy, National and Kapodistrian University of Athens School of Medicine, Athens, Greece
Researcher ID: AAK-6109-2020
ORCID ID: 0000-0002-4831-8005
Google Scholar: Tcs_usIAAAAJ&hl
ResearchGate: Maria Piagkou

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Scopus Author ID: 56210399400
Google Scholar:73VX4NwAAAAJ&hl
ORCID ID: 0000-0003-3215-5982
ResearchGate: Halima Resić

Aldo Rogelis Aquiles Rodrigues, PhD
Department of Physiology, Biological and Natural Sciences Institute, Triangulo Mineiro Federal University, Uberaba, MG, Brazil
ORCID ID: 0000-0001-7017-9147

Domenico Santoro, MD
Full Professor of Nephrology, Chief of Nephrology and Dialysis Unit. Referral Center for "Rare Renal Disease". School of Nephrology, University of Messina, Italy
Researcher ID: L-2482-2013
Google Scholar: OyheJWEAAAAJ
ORCID ID: 0000-0002-4279-6559
ResearchGate: Domenico Santoro

Fatih Sarı, DDS, PhD
Department of Prosthodontics, Faculty of Dentistry, Gaziantep University, Gaziantep, Türkiye
Researcher ID: AAG-5681-2020
ORCID ID: 0000-0002-4818-8562
ResearchGate: Fatih Sarı

Ghada Shahrour, PhD, PMHCNS, RN
Head of Department of Community and Mental Health Nursing, Faculty of Nursing, Jordan University of Science and Technology, Irbid, Jordan
Google Scholar: UTOmj80AAAAJ
ORCID ID: 0000-0002-6929-3361
ResearchGate: Ghada Shahrour

Onur Taydaş, MD
Department of Radiology, Sakarya University School of Medicine, Sakarya, Türkiye
Researcher ID: F-2514-2017
Google Scholar: pkq6z4cAAAAJ&hl
ORCID ID: 0000-0002-9881-7240
ResearchGate: Onur Taydaş

Gregory Tsoucalas, MD, MSc, PhD
Director of the Department of History of Medicine and Medical Deontology, School of Medicine, University of Crete, Heraklion, Greece
ORCID ID: 0000-0002-2595-9686
Google Scholar: dnBJkYwAAAAJ&hl
ResearchGate: Gregory Tsoucalas

Hamit Yıldız, MD
Department of Internal Medicine, Gaziantep University School of Medicine, Gaziantep, Türkiye
Researcher ID: AGU-1325-2022
Google Scholar: o5dsdRIAAAAJ&hl
ORCID ID: 0000-0001-7858-5123
ResearchGate: Hamit Yıldız

Betül Yılmaz Furtun, MD
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Department of Pathology, Anatomy, and Laboratory Medicine (PALM), West Virginia University School of Medicine, Morgantown, WV 26506, USA
Google Scholar: WkBTQlsAAAAJ&hl
ORCID ID: 0000-0002-2578-1128
ResearchGate: Matthew Zdilla

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Editor in Chief: Prof. Ayşe Balat
Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Türkiye
Phone: +90 342 360 60 60
Fax: +90 342 360 16 17
E-mail: info@eurjther.com

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system (e.g. figure 1, figure 2 and figure 3).
The files should not be embedded in a Word document or the main document.
Figures should not be embedded in the manuscript text file.
Figure legends should be listed at the end of the main document.
All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text.
The abbreviation should be provided in parentheses following the definition.

Authors are responsible for the accuracy of references.

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In references, the names of all authors should be written. Usage of "et al" should not be preferred.
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Use abbreviations for journal names. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 15% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article
Yurci A, Gungor ND, Gurbuz T (2021) High Endometrial Thickness Does not Affect IVF/ICSI Outcomes. Eur J Ther. 27(1):94-98. https://doi.org/10.5152/eurjther.2021.20102

Example for Journal Article without English Titles
Aktan-İkiz A, Üçerler H, Orhan M (2007) Anatomic features of fossa navicularis at the skull base and its clinical importance [Kafa iskeletinde fossa navicularis'in anatomik özellikleri ve klinik önemi]. Sendrom 19:34–36 ([In Turkish])

Epub Ahead of Print Articles
Doruk M, Mustafaoglu R, Gül H (2023) The Impact of Using Technological Devices on Mental and Physical Health in Adolescents. Eur J Ther https://doi.org/10.58600/eurjther.20232902-592.y

Book
Anderson DM (2012) Dorland's illustrated medical dictionary, 32nd edn. Saunders Elsevier, Philadelphia

Book chapter
Gray H (1858) Anatomy Descriptive and Surgical 1st edn. In: John W, Parker and Son (eds), London, pp 150-155

Online Document
Bergman RA, Afifi AK, Miyauchi R (2007) Persistent congenital arterial anastomoses. Available from http://www.anatomyatlases.org/AnatomicVariants/Cardiovascular/Images0200/0232.shtml Accessed 22 Jan 2022

Reference citations in the text should be numbered in square brackets. Some examples:

Parent et al. [3] reported that .....
..... on medical radiation [21, 22].
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Corrections, Retractions, Republications and Version Control*

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

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Original Research

Psychological Resilience as a Mediator in the Relationship Between Meaning in Life and Psychological Distress in Adolescents

Berhan Akdağ[1,*], Cansu Ünsal[2], Asiye Arıcı Gürbüz[3]

[1]Department of Child and Adolescent Psychiatry, Silifke State Hospital, Mersin, Türkiye
[2]Department of Psychiatry, Silifke State Hospital, Mersin, Türkiye
[3]Department of Child and Adolescent Psychiatry, Dr. Ekrem Tok Mental Health and Diseases Hospital, Adana, Türkiye

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Corresponding Author
Berhan Akdağ, MD
Address: Department of Child and Adolescent Psychiatry, Silifke State Hospital, Silifke/Mersin, Turkiye
E-mail: drberhanakdag@gmail.com

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ABSTRACT

Objective: Adolescence is marked by significant physical, psychosocial, and cognitive changes. This developmental stage increases vulnerability to mental health challenges, with several mental disorders first manifesting during this period and potentially persisting into adulthood, thus imposing a substantial societal burden. Addressing interventions and protective factors is crucial for enhancing adolescent mental health. However, the role of meaning in life (MIL)—a principal concept in existential psychology for maintaining psychological well-being—has not been thoroughly investigated. This study aimed to explore the relationship between MIL and psychological distress in adolescents, as well as the mediating role of psychological resilience in this relationship.

Methods: The study sample comprised adolescents aged 14 to 17 who were attending a child and adolescent psychiatry outpatient clinic. Data collection occurred through face-to-face interviews between February 2024 and March 2024. The participants completed the Meaning in Life Questionnaire, the Brief Psychological Resilience Scale, and the Patient Health Questionnaire–4.

Results: A total of 113 adolescents participated in the study, with an average age of 16.03 years (SD = 1.19), and 74.3% were female. The findings indicated that the presence of MIL negatively predicted psychological distress (b = –.16 [–.23, –.09], p <.001) and positively predicted psychological resilience (b = .20 [.10, .30], p <.001). Furthermore, psychological resilience completely mediated the association between the presence of MIL and psychological distress (b = –.04 [–.07, –.01]). Gender and age were not related to the presence of MIL, psychological resilience, or psychological distress.

Conclusion: The findings underscore the potential of the presence of MIL to mitigate psychological distress by enhancing psychological resilience. Additional longitudinal studies are necessary to further elucidate the relationship between MIL and mental health in this population.

Keywords: adolescent, meaning in life, psychological distress, psychological resilience

INTRODUCTION

Adolescence represents a period marked by profound changes: hormonal alterations, shifts in the social milieu, and cognitive and emotional development [1]. This phase is also associated with the formation of self-identity [2]. However, adolescence renders individuals particularly susceptible to mental health challenges as they navigate the transition from childhood to adulthood [3]. Numerous mental disorders, including depression, anxiety, and addictive behaviors, often first manifest during this period [4]. These disorders can persist into adulthood, contributing to long-term morbidity and placing a considerable strain on societal resources [3]. It is, therefore, imperative to implement interventions and identify protective factors that can enhance mental health in adolescents.

Adolescents encounter a range of challenges, such as poverty, bullying, and academic pressures [5–7]. Although some adolescents may struggle with these issues and develop mental health problems, the majority are able to navigate these challenges without substantial disruption to their mental health [8]. At this juncture, psychological resilience plays a crucial role in mental health outcomes [9]. Psychological resilience is described as "*the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands*" [10]. Adolescents who are psychologically resilient might experience transient symptoms and fluctuations in their mental health and functioning, but they typically achieve a stable trajectory over time [11]. These individuals are also less likely to suffer from adverse psychological outcomes, such as distress [12]. In contrast, poor resilience is associated with detrimental mental health consequences [13].

Main Points

- Meaning in life refers to the extent to which individuals perceive their lives as having coherence, purpose, or significance.
- Psychological resilience is positively linked to the presence of meaning.
- The presence of meaning is negatively related to psychological distress.
- Psychological resilience mediates the relationship between the presence of meaning and psychological distress.
- Meaning–based interventions can potentially promote both mental health and psychological resilience in adolescents.

Psychological resilience is influenced by various individual and environmental factors, such as cognitive skills, optimism, self-efficacy, and a supportive environment [14]. Another concept central to psychological resilience is "meaning in life" (MIL) [15, 16]. Defining MIL has been challenging, but a common view suggests that it encompasses comprehension, purpose, and existential significance [17]. Comprehension, or coherence, refers to maintaining a consistent understanding of life events. Individuals perceive their lives as meaningful when they integrate their past, present, and future into a coherent narrative [18, 19]. Purpose acts as the guiding force behind an individual's actions and goals, and having goals provides motivation and direction, enabling individuals to experience life as meaningful [20]. Moreover, existential significance is the sense of value and worth one attaches to their own life and the precursors of MIL judgments [21].

Previous studies emphasize the role of MIL in enhancing psychological well-being [22]. Individuals with a higher sense of meaning generally report lower levels of psychological distress [23], while a lack of meaning is associated with a greater risk of adverse mental health outcomes, such as depression and suicidal ideation [24]. However, existing research presents gaps that necessitate further exploration. Therefore, this study examines the relationship between the presence of meaning and psychological distress among adolescents and hypothesizes that psychological resilience mediates this relationship.

MATERIALS AND METHODS

Power Analysis

A power analysis was performed *a priori* using standard software [25]. This analysis included four predictors and used 0.15 as the effect size (f^2), 0.80 as the power, and 0.05 as the significance level [26]. The results were then compared with a conventional formula (N = 104 + K, where K is the number of predictors) [27], establishing a minimum required sample size of 108 participants.

Participants and Procedure

The participant cohort consisted of adolescents aged 14–17 who were attending the Child and Adolescent Psychiatry Outpatient Clinic at Silifke State Hospital in Mersin, Türkiye. Data collection occurred through face-to-face interviews based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria from February to March 2024. Before obtaining written informed consent, the study procedures were fully explained to

the adolescents and their parents during the interviews. A total of 113 adolescents agreed to participate in the study, representing a subsample of the 167 interviewed adolescents (participation rate = 67.7%). Fifty-four adolescents were excluded due to having a psychiatric diagnosis (e.g., psychosis and bipolar disorder) or neurodevelopmental disorders (e.g., intellectual disabilities, autism spectrum disorder, and specific learning disabilities), as well as refusing to participate in the study.

Data Collection Tools

The Meaning in Life Questionnaire (MLQ−10) is designed to evaluate two key aspects of meaning in life: the *presence of meaning* and the *search for meaning* [28]. The first (MLQ–PoM) measures how much individuals perceive their lives as meaningful and purposeful. The second examines how actively people seek to understand the purpose of their lives [28]. The MLQ consists of 10 statements, with five dedicated to each dimension. Examples of these statements include *"I understand my life's meaning"* for the presence of meaning and *"I am searching for meaning in my life"* for the search for meaning. Respondents rate these statements on a 7-point Likert scale, ranging from *"1 = absolutely untrue"* to *"7 = absolutely true."* Scores for each dimension can range from 5 to 35, with higher scores indicating a greater sense of meaning or a more active search for it. The MLQ has been widely used in various research settings and translated into several languages, including Turkish. It has been validated and is considered reliable for measuring meaning in life among Turkish populations [29, 30].

The Brief Psychological Resilience Scale (BPRS) was created to measure an individual's overall psychological resilience [31]. The BPRS consists of six items, including statements like *"I tend to bounce back quickly after hard times"* and *"It is hard for me to snap back when something bad happens."* Participants rate these items using a 5-point Likert scale, ranging from *"strongly disagree"* to *"strongly agree,"* with certain items (specifically 2, 4, and 6) being scored in reverse. The total score can range from 6 to 30, where higher scores indicate greater psychological resilience. Previous studies have established the BPRS as a reliable and valid measure of psychological resilience in Turkish populations [32].

The Patient Health Questionnaire–4 (PHQ–4) is a four-item instrument developed to evaluate psychological distress among respondents [33]. It includes two items that focus on depression (PHQ–2) and two that address anxiety (GAD–2), both of which have proven effective as short screening instruments. The PHQ–4 employs a 4-point Likert scale, where responses range from *"0 = not at all"* to *"3 = nearly every day."* Sample items include *"Feeling nervous, anxious, or on edge"* and *"Feeling down, depressed, or hopeless."* The total score can range from 0 to 12, with no reverse scoring applied. Higher scores reflect greater psychological distress. The PHQ–4 has also been confirmed as a reliable and valid measure for assessing psychological resilience in Turkish samples [34].

Statistical Analysis

Statistical analyses were conducted using SPSS 29.0. The normality assumption was evaluated using skewness and kurtosis values and histogram examination, with skewness and kurtosis values within ±1.0 indicating normal distribution [35]. Pearson's correlation analysis was employed to explore the relationships between variables. Additionally, a mediation analysis was performed to assess the role of psychological resilience as a mediator in the relationship between the presence of meaning and psychological distress [36]. Age and gender were included as covariates [37], but psychiatric diagnoses were not controlled for due to their categorical heterogeneity and the small size of each category.

RESULTS

A total of 113 adolescents participated in the study, with an average age of 16.03 years (SD = 1.19), and 74.3% were female (n = 84). Out of the participants, 61.9% (n = 70) had been diagnosed with a psychiatric condition. Anxiety disorders were the most prevalent psychiatric diagnosis (18.6%, n = 21), followed by depressive disorders (12.4%, n = 14), attention deficit hyperactivity disorder (10.6%, n = 12), and other conditions such as obsessive-compulsive disorder and bulimia nervosa (Table 1). Unpaired *t*-test analyses revealed no significant differences in scale scores based on gender, education status, or chronic diseases. Likewise, no differences were observed in scale scores based on psychiatric diagnosis.

A significant negative correlation was observed between MLQ–PoM and PHQ–4 scores (r = –.402, p <.001). Similarly, an inverse association was found between BPRS and PHQ–4 scores (r = –.387, p <.001). In contrast, MLQ–PoM and BPRS scores demonstrated a positive correlation (r = .372, p <.001) (Table 2).

Table 1. The sociodemographic characteristics (n = 113)

Age (years), mean (SD)	16.03 (1.19)
Gender, *n (%)*	
Female	84 (74.3)
Male	29 (25.7)
Educational status, *n (%)*	
Formal education	89 (78.8)
Non-formal education	24 (21.2)
Chronic disease, *n (%)*	
No	90 (79.6)
Yes	23 (20.4)
Psychiatric diagnosis, *n (%)*	
No diagnosis	43 (38.1)
Anxiety disorders	21 (18.6)
Depressive disorders	14 (12.4)
Attention deficit hyperactivity disorder	12 (10.6)
Others	23 (20.4)

SD: Standard deviation

Table 2. The correlations among variables

Variables	1	2	3	Mean	SD	Skew.	Kurt.	α
The presence of meaning (MLQ–PoM)	—			20.91	6.92	–.198	–.669	0.75
Resilience (BPRS)	.372***	—		15.67	3.06	–.062	–.790	0.62
Psychological distress (PHQ–4)	–.402***	–.387***	—	8.05	2.86	–.389	–.898	0.73

****p <.001, Pearson correlation analysis, Kurt: Kurtosis, SD: Standard deviation, Skew: Skewness, MLQ–PoM: Meaning in Life Questionnaire–The Presence of Meaning Subscale, BPRS: Brief Psychological Resilience Scale, PHQ–4: Patient Health Questionnaire–4*

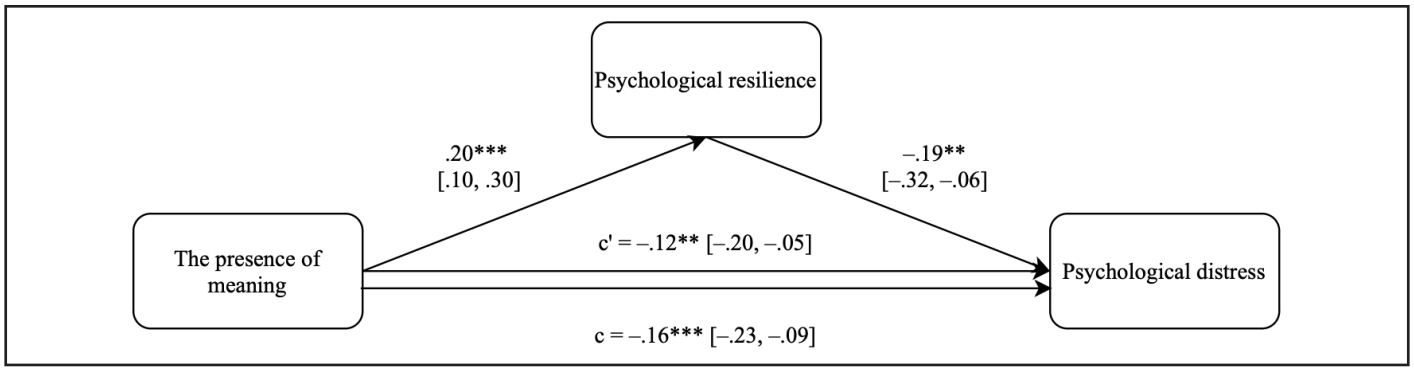

Figure 1. Conceptual and statistical diagram, **p <.01, ***p <.001.

Mediation Analysis

There was a significant positive association between the presence of meaning and psychological resilience (*b* = .20, 95% CI [.10, .30], *p* <.001). Concurrently, psychological resilience was found to be inversely related to psychological distress (*b* = –.19, 95% CI [–.32, –.06], *p* = .006) (Figure 1).

The presence of meaning exerted a significant negative direct effect on psychological distress (*b* = –.12, 95% CI [–.20, –.05], *p* = .002) as well as a total effect (*b* = –.16, 95% CI [–.23, –.09], *p* <.001). The mediating role of psychological resilience in the relationship between the presence of meaning and psychological distress was also statistically significant (*b* = –.04, 95% CI [–.07, –.01]) (Figure 1).

DISCUSSION

The current study demonstrates that the presence of meaning is inversely associated with psychological distress, and psychological resilience mediates this relationship. These findings are compatible with the existing literature [38, 39]. It is beneficial to consider these results in the context of the key aspects of MIL, coherence, purpose, and existential significance. The sense of coherence (SoC) theory posits that individuals with a higher sense of coherence are more adept at managing emotional distress, thereby reducing the likelihood of mental health issues [40]. Furthermore, a strong sense of coherence enhances an individual's ability to understand situations, effectively utilize personal resources, and develop suitable coping strategies [41]. Supporting this, a longitudinal study revealed that SoC scores at the age of 15 negatively predicted the relative risk of psychiatric diagnosis at the age of 18 [42]. Another longitudinal study reported a notable difference in social functioning and mental health indicators between adolescents with low and high SoC, favoring those with high SoC [43].

Possessing a profound purpose in life enhances the ability to cope with negative events, bolsters psychological resilience, and expedites emotional recovery following adverse experiences [44, 45]. Conversely, a lack of purpose is associated with the emergence of mental health challenges [46]. Moreover, a sense of meaning, including purpose and coherence, can shield against psychological distress by diminishing repetitive negative thinking and uncertainty [47]. Indeed, an epidemiological study demonstrated that over a 4-year follow-up period, individuals with a stronger sense of purpose experienced significantly positive psychosocial outcomes (e.g., higher optimism, reduced risk of depression, and lower loneliness), as well as improved physical health outcomes, such as a reduced risk of mortality [48]. Similarly, a longitudinal study showed that increases in purpose identification promoted life satisfaction and reduced depressive symptoms in adolescents [49].

Existential significance arises from the internal recognition of one's life having enduring influence over time and space [50]. It, along with other MIL components, is linked to favorable mental health indicators. While the belief in one's significant impact on the world may initially appear to be a form of narcissistic delusion, there is no substantial evidence to suggest that this sense of importance results in negative mental health outcomes [20]. Furthermore, fostering a sense of existential significance is crucial for preventing serious consequences such as suicidal thoughts and attempts [51] and is positively correlated with self-esteem, which is predictive of beneficial social and psychological outcomes [52–54]. Conversely, social exclusion and threats to belongingness can negatively predict mental health by reducing a sense of significance [55].

This study also revealed the mediating role of psychological resilience in the relationship between the presence of meaning and psychological distress, aligning with existing literature. Resilience refers to the capacity to withstand, adapt to, recuperate from, and thrive despite challenging life situations [56]. Extensive research indicates a negative connection between psychological resilience and distress [57]. Furthermore, the presence of MIL is linked to favorable mental health outcomes, such as reduced psychological distress [58]. This link could be attributed to increased resilience, as perceiving life as meaningful can improve coping with adverse events and enhance psychological resilience.

Various demographic factors have been associated with MIL. Females are more inclined than males to experience, contemplate, and prioritize the significance of and meaning. Therefore, females demonstrate a greater determination to seek meaning in their lives and possess a stronger sense of meaning compared to males [38]. The current findings do not support this suggestion. Additionally, some studies have demonstrated that a sense of meaning tends to increase consistently from the age of 25 onwards, while other studies propose that the relationship between age and meaning in life is nonlinear [59]. In this study, there is no significant relationship between the presence of meaning scores and age. As observed, these findings diverge from earlier studies regarding the link between demographic factors and meaning in life, which may be attributed to the limited sample size in this research.

This study offers valuable insights into the relationship between the presence of meaning and psychological distress. However, it is essential to acknowledge certain limitations. The cross-sectional design precludes the ability to observe changes in the variables over time. Secondly, the small sample size and clinical sampling may limit the generalizability of the findings. Thirdly, the relationships of MIL components (i.e., comprehension, purpose, and existential significance) with psychological resilience and psychological distress were not evaluated separately. Additionally, concepts such as optimism, social support, and cognitive skills that are linked to psychological resilience and distress were not addressed.

CONCLUSION

The findings from this study underscore the inverse association between the presence of meaning and psychological distress. Adolescence plays a critical role in human development, making it essential to discern the root causes of psychological distress during this developmental stage. This research supports the implementation of practical interventions aimed at improving mental health among adolescents. Encouraging adolescents to discover meaning and purpose in their lives could significantly mitigate mental health challenges. Thus, interventions focused on meaning could enhance mental health [60, 61]. Moreover, engaging in leisure activities may promote adolescents' mental health by enabling them to experience life more meaningfully [62]. Additional longitudinal studies are necessary to thoroughly explore the relationship between MIL and mental health.

Conflict of Interest: No conflict of interest was declared.

Informed Consent: Informed consent was obtained from all participants and their parents.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions: Conception: BA, CÜ; Design: BA, CÜ, AAG; Supervision: AAG; Fundings: BA; Materials: BA, CÜ; Data Collection and/or Processing: BA; Analysis and/or Interpretation: BA, AAG; Literature review: BA, CÜ, AAG; Writing: BA, CÜ; Critical Review: BA, CÜ, AAG. All authors approved the final version of the manuscript.

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Original Research

The Impacts of Chronotype on Sleep Quality, Eating Attitudes, and Cardiovascular Risk in Patients with Bipolar Disorder

Beyza Erdoğan Aktürk[1,*], Eda Aslan[2], Ayşe Erdoğan Kaya[3]

[1] Department of Psychiatry, Tarsus State Hospital, Mersin, Türkiye
[2] Department of Psychiatry, Mersin University Faculty of Medicine, Mersin, Türkiye
[3] Department of Psychiatry, Hitit University Corum Erol Olcok Training and Research Hospital, Corum, Türkiye

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Corresponding Author
Beyza Erdoğan Aktürk, MD
Address: Department of Psychiatry, Tarsus State Hospital, Mersin, Türkiye
E-mail: beyzaerdogan128@gmail.com

ABSTRACT

Objective: The study aimed to investigate the relationship between chronotype and sleep quality, eating attitudes and cardiovascular disease (CVD) risk in bipolar disorder (BD).

Methods: The study included data on sociodemographic and clinical variables, anthropometric measurements, and blood biochemical tests of 78 individuals in the euthymic period diagnosed with BD. Morningness-Eveningness Questionnaire (MEQ), Pittsburgh Sleep Quality Index (PSQI), and Eating Attitudes Test-40 (EAT-40) were administered to the participants. The internet-based Systematic Coronary Risk Evaluation-2 (SCORE-2) calculator was used as a cardiovascular risk assessment tool, and the presence of metabolic syndrome (MetS) was assessed.

Results: Participants were divided into three chronotype groups: morning (n=25, 32.1%), intermediate (n=26, 33.3%) and evening type (n=27, 34.6%). The evening chronotype had significantly higher systolic blood pressure levels compared to the morning chronotype (p=0.050). Lower HDL (High-Density Lipoprotein) levels were observed in the evening chronotype group, while there was no significant difference in other biochemical parameters. 89% of the evening group had poor sleep quality. Two thirds of individuals in the evening group had MetS. After adjusting for confounding factors, it was observed that evening-type individuals had higher SCORE-2 scores compared to the non-evening-type group.

Conclusion: In conclusion, late chronotype in BD is associated with poorer clinical prognosis and sleep quality, unhealthier dietary habits and higher risk of CVD. The development of chronobiological treatment interventions targeting circadian regulation may be beneficial for evening chronotype diagnosed with BP.

Keywords: Bipolar Disorder, Cardiovascular Risk, Chronotype, Eating Attitudes, Metabolic Syndrome, Sleep Quality

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INTRODUCTION

The emphasis on circadian and chronobiological mechanisms in the etiopathogenetic of various psychopathologies, especially bipolar disorder (BD) is noteworthy [1, 2].

Studies have shown that, in the general population, a late chronotype is associated with poorer sleep quality, cigarette/alcohol/caffeine dependence, unhealthy eating habits a sedentary lifestyle and an increased risk of cardiometabolic disease [3-5]. Disturbances in sleep and biological rhythms, especially in people who are vulnerable, can lead to mood swings and depressive symptoms, which are more common in people with an evening chronotype [6].In patients with BD, the evening chronotype is more prevalent compared to the healthy population, and it is thought that a late chronotype is associated with poorer disease outcomes and reduced functional levels [7, 8]. The nature of BD, medication treatments and many co-morbid conditions can cause disruptions in circadian rhythms, which can lead to a variety of sleep disturbances [6]. Poor sleep quality has been shown to have a negative impact on the treatment process and is a poor prognostic factor for patients diagnosed with BD, as well as being associated with reduced functionality and quality of life [9]. Additionally, sleep disorders are associated with increase increase the risk of cardiovascular and metabolic disease [10].
The circadian system regulates many aspects of eating behavior, including the rhythm of hunger, timing of meals, and food preferences [11]. Disruptions in the sleep-wake cycle can lead to metabolic dysfunctions such as a decrease in the appetite-regulating anorexigenic hormone "leptin," resulting in overeating behaviour and ultimately obesity [12]. It has been shown that individuals with poor sleep quality and a late chronotype tend to have poor dietary habits [3, 13].

Main Points

- BD patients with an evening chronotype have poorer sleep quality and worse eating habits.
- BD patients with an evening chronotype have higher blood pressure values and a greater frequency of metabolic syndrome, while their HDL levels are lower.
- CVD risk is higher in BD patients with an evening chronotype compared to the non-evening chronotype group.
- Evening chronotype appears to be associated with a higher cardiovascular risk in patients diagnosed with BD.

Co-diagnosis of eating disorders with various psychiatric diagnoses is commonly encountered. Patients with comorbid eating disorders and BD are at increased risk of obesity, cardiovascular diseases (CVD), type 2 diabetes mellitus (DM), hyperlipidemia, and cerebrovascular disease increases [14]. Studies investigating the relationship between unhealthy eating attitudes and chronotype in BD patients are scarce.

In patients diagnosed with BD, CVD are among the leading medical conditions that shorten life expectancy. Patients have approximately twice the risk of CVD and metabolic syndrome (MetS) compared to the general population [15]. Various factors have been identified as potential contributors to the relationship between BD and increased risk of CVD. Sedentary lifestyle, endocrine disorders, dysregulations in the sympathetic nervous system, stress burden, disorders in the hypothalamic-pituitary-adrenal (HPA) axis, side effects of medications, reduced access to general health services, high rates of tobacco use, and unhealthy eating habits are among them [15-18].

It has been suggested that the chronotype, particularly the evening chronotype, is one factor associated with an increased risk of CVD [19]. It is thought that evening chronotypes may develop a set of behavioural and physiological risk factors due to chronic misalignment between internal physiological timing and the timing of external work and social activities, making them particularly vulnerable to CVD [20].

The high frequency of CVD risk factors and MetS observed in these patients imposes an additional medical burden, complicates the treatment process, reduces overall physical well-being and functionality, worsens quality of life, diminishes self-esteem, and negatively impacts psychological well-being, thereby adversely affecting the course of BD [21]. Investigating chronobiological mechanisms that may contribute to the increased risk of CVD in BD and better understanding factors that could serve as potential targets for treatments and interventions will contribute to preventing metabolic and cardiovascular problems that shorten lifespan in these patients. Exploring chronobiological mechanisms that may contribute to increased CVD risk in BD and better understanding of factors that could serve as potential targets for treatments and interventions will contribute to the prevention of metabolic and cardiovascular problems that shorten lifespan in these patients.

The aim of this study is to explore the direct and indirect effects of chronotypes, sleep quality, and dietary habits on CVD risk in euthymic patients diagnosed with BD.

MATERIALS AND METHODS

Study Design and Participants

This study was designed as a cross-sectional study and was conducted on 78 volunteer patients attending the outpatient psychiatric clinic who were in regular treatment and diagnosed with BD according to DSM-5 criteria. Inclusion criteria for the study were being between 18 and 65 years of age, being able to communicate verbally on the scales used, being in euthymic phase for at least 8 weeks. Exclusion criteria for the study were being in an acute mood episode, having a comorbid neurological or neurodevelopmental disorder, having a history of alcohol or substance use disorder within the previous six months, having language and communication problems, lack of education to understand the tests, and pregnancy. Ethical approval for the study was obtained from Mersin University Clinical Research Ethics Committee on 3 November 2021 with protocol number 2021/685. Our research was conducted in accordance with the Helsinki Declaration of 1964. All participants provided written informed consent.

Assesments of Socio-Demographic and Clinical Parameters

- A socio-demographic and clinical data form was used to collect descriptive information and clinical characteristics related to BD. Participants' exercise habits were assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [22] and their dietary attitudes were assessed using questions prepared by the clinician.
- Pittsburgh Sleep Quality Index (PUQI) is a tool that includes seven subscales used to evaluate sleep quality [23]. A total score of 5 or higher indicates poor sleep quality. The Turkish validity and reliability study of the scale was conducted by Ağargün et al. [24]
- Morningness-Eveningness Questionnaire (MEQ) is developed by Horne and Ostberg [25] and includes questions about sleep-wake patterns and the timing of their physical and psychological performances. The validity and reliability study of the scale in Turkey was conducted by Ağargün and colleagues [26].
- Eating Attitudes Test-40 (EAT-40) developed to assess disturbances in eating behaviour [27]. The Turkish validity and reliability study was conducted by Savaşır et al. [28]. Individuals with a score 30 or above are classified as having " predisposition to eating disorder".

Assesments of Anthropometric, Vital, Biochemical Parameters

- Participants' weight, height, waist-to-height ratio, BMI, and blood pressure values were measured and recorded. Those with a BMI value of 30 and above were considered obese.
- Fasting blood glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride and total cholesterol levels in mg/dL obtained from routine biochemical tests performed after a 12-hour fast within the previous 3 months were retrospectively recorded.

Assesment of Metabolic Syndrome and Cardiovascular Risk

- The study used both a web-based risk calculator and the presence of metabolic syndrome (MetS) to determine participants' risk of CVD.
- SCORE-2 (Systematic Coronary Risk Evaluation-2) Calculation Tool is an internet-based tool, which calculates the risk of fatal CVD within 10 years, was first developed in 2007. It takes into account gender, smoking status, age, blood pressure, and total cholesterol levels [29].
- Metabolic Syndrome (MetS) is considered a significant predictor of CVD. In our study, the presence of MetS was assesed according to the diagnostic criteria of the National Cholesterol Education Program, Adult Treatment Panel III .

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were summarized as counts, percentages, means, standard deviations, medians and minimum-maximum values. Chi-square tests were used to determine differences in frequencies between categorical groups. For dependent variables with a normal distribution, Student's t-tests and ANOVA tests were used for analyses between two independent groups. Tukey's test was used for post hoc analyses. For continuous variables with non-normal distribution, Mann-Whitney U test and Kruskal-Wallis test were used for comparisons between two groups. The Spearman correlation test was used for correlation analysis. The ANCOVA test was used to determine the factors

predicting the CVD risk score. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

A total of 78 patients were included in the study. The mean age of the participants was 41.06 ± 12.07 years. According to their scores on MEQ, the participants were categorized into three chronotype groups: morning type (n=25, 32.1%), intermediate type (n=26, 33.3%), and evening type (n=27, 34.6%). The sociodemographic and clinical characteristics of the participants according to their chronotypes are summarized in Table 1.

There were no significant differences between groups for height, weight, waist circumference, waist to height ratio, BMI. Mean systolic blood pressure was significantly higher in the evening group than in the morning group ($\chi2=5.699$; $p=0.050$). Mean diastolic blood pressure was also higher in the evening group compared to the other groups, but this difference was not statistically significant ($\chi2=5.927$; $p=0.052$). The frequency of MetS was observed to be lowest in the morning group, followed by the intermediate type, and highest in the evening group; the differences between all groups were found to be statistically significant ($\chi2=9.816$, $p=0.007$). Anthropometric measurements and blood biochemical tests were separately analyzed for men and women; no significant differences were observed between chronotype groups. Anthropometric measurements, blood biochemical parameters and numerical characteristics related to metabolic and CVD risk of the participants are shown in Table 2.

The frequency of paying attention to the food satiation was significantly lower in evening chronotypes compared to morning chronotypes ($\chi2=10.219$; $p=0.003$). No significant differences were observed between chronotype groups in terms of main mail and snack consumption, preferred food characteristics, EAT-40 scores, and predisposition to eating disorders. The frequency of having good sleep quality was significantly higher in intermediate chronotypes (42.3%, n=11) than in the morning chronotypes (84%, n=21) and evening chronotypes ($\chi2=27.983$; $p<0.001$). Poor sleep quality was observed in the majority of evening types (88.9%, n=24). A significant increase in the PSQI total score was observed from morning individuals to evening types (higher scores indicate poorer sleep quality) ($\chi2=21.328$; $p<0.001$). Among the PSQI subscales, scores of evening chronotype were significantly higher than the morning chronotype group for subjective sleep quality, sleep latency, sleep medication, and daytime sleep dysfunction subscales (p values: 0.016; <0.001; 0.002; 0.004). No significant differences were observed between groups in terms of other dimensions of PSQI such as sleep duration, habitual sleep efficiency, and sleep disturbance scores. Participants' eating habits, EAT-40 scores, PSQI and subscale scores are shown in Table 3.

Table 1. Mean values (± SD) and percentages (%) of sociodemographic and clinical data according to the chronotypes

	Total n=78 (100%)	**Chronotype**			
		Morning n=25 (100%)	**Intermediate n=26 (100%)**	**Evening n=27 (100%)**	***p***
Age, year	41,06 ± 12,07	42,68 ± 12,519	42,81 ± 12,303	37,89 ± 11,175	0,242
Male, %	50	40	42,3	66,7	0,990
Marital status, %					
Single	39.7	28	30,8	59,3	0,059
Married	44,9	48	50	37	
Divorced	15,4	24	19,2	3,7	
Smoking rates, %	42,3	32	34,6	59,3	0,860
Exercise habits[1], %					
Sedentary	60,3	60	50	70,4	0,626
Moderately active	16,7	16	19,2	14,8	
Active	23,1	24	30,8	14,8	

[1:] Classified according to the GLTEQ.

MEQ: Morningness-Eveningness Questionnaire, SD: Standard Deviation

Table 2. Anthropometric measurements, blood biochemical tests and CVD risk for chronotypes presented as mean ± SD, percentage (%) or median (range) values

	Total n=78 (100%)	**Chronotype**			
		Morning n=25 (100%)	**Intermediate n=26 (100%)**	**Evening n=27 (100%)**	***p***
Height (cm)	167,7 ± 8,1	166,4 ± 7,7	167 ± 8,2	169,8 ±8,3	0,272
Weight (kg)	85,3 ± 14	81,5 ± 13,1	87,2 ± 17	87,1 ± 11,1	0,247
Waist circumference (cm)	106,1 ± 14	103,3 ± 12,6	108,5 ± 18	106,4 ± 10,6	0,453
Waist-to-height ratio	0,63 (0,46-0,93)	0,63 (0,47-0,75)	0,64 (0,46-0,93)	0,62 (0,49-0,79)	0,683
BMI (kg/m^2)	30,5 ± 5,5	29,4 ± 4,2	31,6 ± 7,5	30,3 ± 4,2	0,415
Obesity, %	57,7	52	53,8	66,7	0,814
Blood pressure (mmHg) Systolic Diastolic	 125 (100-180) 80 (60-100)	 117 (100-150) 79 (60-90)	 125 (100-150) 80 (67-100)	 130 (110-180) 85 (60-100)	 **0,050** 0,052
Fasting blood sugar (mg/dL)	102,2 ± 26,4	102,9 ± 28	104,9 ± 33,9	98,9 ± 14,6	0,811
HDL (mg/dL)	49,5 ± 11,7	50,7 ± 13,2	51,2 ± 11,7	45,9 ± 9,7	0,149
LDL (mg/dL)	112,5 ± 41,5	113,7 ± 44,4	99,6 ± 40,9	107,8 ± 40,2	0,760
Triglycerides (mg/dL)	167,6 ± 100,1	157,8 ± 85,3	146,2 ± 69,1	197,1 ± 130	0,320
Total cholesterol (mg/dL)	195,8 ± 52,2	197,9 ± 52,7	197,8 ± 50	197,7 ± 57,7	0,962
CVD risk score[1]	2,5 (0,3-16)	2,1 (0,4-8,2)	2,45 (0,3-16)	3,6 (0,7-15,4)	0,289
MetS presence, %	42,3	20	42,3	63	**0,007**

BMI: Body Mass Index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MetS: Metabolic Syndrome.

[1]: Estimated CVD risk (according to SCORE-2).

Table 3. Mean ± SD, percentage (%) or median (range) values of participants' eating attitudes and sleep quality-related data according to chronotypes

	Total n=78 (100%)	**Chronotype**			
		Morning n=25 (100%)	**Intermediate n=26 (100%)**	**Evening n=27 (100%)**	***p***
Regular main meal consumption, %	80,8	88	80,8	74,1	0,445
Regular snack consumption%	55,1	64	65,4	37	0,065
Characteristics of preferred foods, % Easily prepared Healthy cooking method Low in fat content Low-calorie Satiation of food Delicious meal Balanced content meal Vegetarian/vegan/gluten-free foods Free from additives Economical foods	 65,4 59 52,6 42,3 87,2 92,3 74,4 5,1 61,5 70,5	 76 72 68 56 100 100 84 8 80 72	 61,5 57,7 53,8 38,5 92,3 92,3 73,1 0 53,8 69,2	 59,3 48,1 37 33,3 70,4 85,2 66,7 7,4 51,9 70,4	 0,394 0,215 0,081 0,227 **0,003** 0,157 0,354 0,459 0,07 0,977
EAT-40	15,5(2-46)	14 (5-43)	14 (3-39)	19 (2-46)	0,736

Predisposition to eating disorders, % (30≤EAT-40)	20,5	24	15,4	22,2	0,713
PSQI score					
Subjective sleep quality	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-2)	**0,016**
Sleep latency	1 (0-3)	1 (0-2)	1 (0-3)	2 (0-3)	**<0,001**
Sleep duration	0 (0-3)	0 (0-1)	0 (0-3)	0 (0-3)	0,931
Habitual sleep efficiency	0 (0-3)	0 (0-3)	0 (0-3)	0 (0-3)	0,434
Sleep disturbances	1 (0-3)	1 (0-2)	1 (0-2)	1 (0-3)	0,552
Sleep medication	0 (0-3)	0 (0-3)	0 (0-3)	3 (0-3)	**0,002**
Daytime sleep dysfunction	0,5 (0-3)	0 (0-2)	1 (0-3)	1 (0-3)	**0,004**
Total	5 (2-46)	3 (5-43)	5 (3-39)	8 (2-46)	**<0,001**
Sleep Quality, %					
High (PSQI<5)	44,9	84	42,3	11,1	**<0,001**
Poor (PSQI≥5)	55,1	16	57,7	88,9	

PSQI: Pittsburgh Sleep Quality Index, EAT-40: Eating Attitudes Test-40

Table 4. Mean ± SD, percentage (%) or median (range) values of data for non-evening and evening chronotypes

	Chronotype		
	Non-evening n=51 (100%)	**Evening n=27 (100%)**	**p**
Male, %	41.2	67.7	**0.032**
Smoking, %	33.3	59.3	**0.027**
Blood Pressure (mmHg)			
Systolic	120 (100-150)	130 (110-180)	**0.005**
Diastolic	80 (60-100)	85 (60-100)	**0.042**
HDL (mg/dL)	53.6 ± 12.3	45.9 ± 9.7	**0.050**
MetS presence, %	31.4	63	**0.007**
Regular main meal consumption, %	64.7	37	**0.019**
Preference for low-fat foods, %	60.8	37	**0.046**
Preference for satisfying foods, %	96.1	70.4	**0.001**
PSQI score			
Subjective sleep quality	1 (0-3)	1 (0-2)	**0.003**
Sleep latency	1 (0-3)	2 (0-3)	**<0.001**
Sleep medication	0 (0-3)	3 (0-3)	**0.002**
Daytime sleep dysfunction	0 (0-3)	1 (0-3)	**0.005**
Total	4 (0-17)	8 (1-15)	**<0.001**
Sleep Quality			**<0.001**
High (PSQI<5)	62.7	11.1	
Poor (PSQI≥5)	37.3	88.9	

Table 5. The effect of evening or non-evening group on cardiovascular disease risk score (when age variable is controlled)

	Chronotype	
	Non-evening	**Evening**
CVD risk score		
x̄	3,34	4,48
SD	3,21	3,89
CVD risk score [adj]		
x̄	3,04	5,04
SE	0,39	0,54

The common variable in the model is accepted as age = 41.06.
CVD risk score was calculated using the SCORE-2 prediction algorithm.
CVD risk score [adj:] Age-adjusted CVD risk score was calculated using the SCORE-2 prediction algorithm.
x̄: Mean, SD: Standard deviation, SE: Standard Error

After dividing the participants into two categories as evening-type and non-evening-type, analyses were repeated. According to the analysis, evening-types comprised 34.6% (n=27) of the total group, while non-evening-types comprised 65.4% (n=51). The variables that revealed significant differences between the non-evening and evening groups are shown in Table 4.

In the analysis of covariance performed by controlling for age, one of the variables used to calculate the CVD risk score. It was observed that being in the evening group had a significant effect on the CVD risk score, the mean CVD risk score was higher in the evening group independent of the age variable: F (1,75) = 8.812; p=0.004; r: 0.11 (Table 5).

DISCUSSION

The current study investigated the clinical characteristics according to chronotype in patients diagnosed with BD, as well as exercise habits, sleep quality and dietary attitudes, and their effects on CVD risk.

In this study, consistent with the literature [30], the frequency of smoking in the BD group was observed to be higher in the evening chronotype, similar to that in the general population [3, 5]. The increased incidence of impulsivity and risk-taking behaviour with in BD patients who have evening chronotype may be the cause of various addictions, particularly tobacco [31]. Approximately 60% of participants were sedentary, but no significant difference in levels of physical inactivity was observed between the chronotype groups in our research.

Approximately 21% of participants were observed to have a predisposition to eating disorders, with no difference observed between the chronotype groups in terms of eating disorders. However, consistent with the literature, evening types were observed to have irregular snacking habits, to consume more fatty foods and to pay less attention to eating a satisfying diet [8, 13].

In our study, individuals' height, weight, waist circumference, waist-to-height ratio and BMI did not differ according to chronotype. Some studies in the literature associate eveningness with overweight and obesity [32]. There are also studies in the literature that found no differences in waist circumference, BMI and obesity prevalence between chronotype groups [3, 8, 30]. In our study, an increase in both systolic and diastolic blood pressure was observed with chronotype. According to a clinical study by Godin et al, while no difference in systolic blood pressure was found between chronotype groups, it was observed that patients with diastolic blood pressure above 70 mmHg were clustered in the evening chronotype [30].

In a study of patients with BD by Romo-Nava et al, the frequency of hypertension was 18%, which was significantly higher than in the non-evening group. In our study, the frequency of meeting the diagnostic criteria for HT on repeated measurements was found to be twice as high in the evening types (41%) as compared to the non-evening types (20%) [8]. Although no significant differences were observed in the other biochemical parameters, it was detecte that HDL levels were higher in the group of non-evening types. According to a meta-analysis of 27 community-based studies, a late chronotype was associated with a higher BMI, higher levels of LDL and total cholesterol, and lower levels of HDL [33]. In a study of patients diagnosed with BD by Godin et al, no differences in LDL levels were observed between the chronotype groups. However, low HDL levels and hypertriglyceridemia were more common in the evening type group [30]. Factors such as higher prevalence of smoking, physical inactivity, preference for high-calorie and irregular diet, more frequent occurrence of depressive symptoms and stress burden, and increased frequency of smoking in patients with evening-type BD may predispose them to higher blood pressure, obesity, and low HDL levels. Further research is needed to investigate the relationship between biochemical parameters and chronotype in patients with BD in larger studies. According to our findings, almost 9 out of 10 evening types reported poor sleep quality. This rate was 2.5 to 3 times higher

than in the non-evening group. Previous studies have also associated the evening chronotype with poorer sleep quality [30]. Previous studies have shown that short sleep duration and sleep disorders are associated with dyslipidemia, obesity, coronary heart disease, and myocardial infarction. [34, 35].

On the basis of this study, a remarkable relationship was observed between eveningness and CVD risk score. In addition, about two-thirds of patients in the evening-type group had MetS, which was significantly higher compared to other chronotype groups. Studies examining CVD risk scores by chronotype in patients with BD using comprehensive parameters are inadequate. In their study of 752 BD patients, Godin et al. found that the plasma atherogenic index was higher in the evening-type group [30]. Previous studies have used different methods to calculate CVD risk scores using different parameters, making it difficult to compare results between studies. However, both the results of our study and publications in the literature suggest an association between eveningness and increased CVD risk score in people diagnosed with BD. There are several hypotheses regarding the relationship between evening chronotype, poor sleep quality and cardiometabolic risk. For example, increased appetite hormones caused by circadian misalignment are thought to be associated with increased CVD risk [12]. It is also known that circadian disruption may contribute to impaired glucose tolerance and reduced insulin sensitivity [36]. Furthermore, it should be remembered that poor sleep quality and insufficient sleep have negative effects on metabolism and may contribute to increased blood pressure, impaired insulin metabolism and increased CVD risk through their association with stress and their effects on dopaminergic pathways. Other behavioural factors, such as lower levels of physical activity, smoking or alcohol consumption, and unhealthy dietary habits in evening types, may also contribute to the association between chronotype and cardiometabolic disease. These observations are not specific to BD and are applicable to the general population. The circadian system, which plays a role in regulating the HPA axis, leptin/ghrelin hormone balance, and components of immune and oxidative stress, and abnormalities in this system have been proposed as factors triggering metabolic problems in patients diagnosed with BD [37]. Moreover, BD is considered to be a multisystemic inflammatory disorder that disrupts hormonal, metabolic and circadian homeostasis [17, 38]. In addition, genome-wide association studies, including meta-GWAS, have found that genes encoding key components associated with circadian alignment or circadian signalling pathways overlap with genetic traits observed in mood disorders and cardiometabolic diseases [33]. It is thought that the disrupted circadian system in patients with BD controls the expression of numerous genes regulated by both central and peripheral clocks that play a role in cortisol secretion, glucose homeostasis, blood pressure or lipid regulation [39]. Furthermore, the use of atypical antipsychotics and the prevalence of polypharmacy in patients with BD may induce both sedation and weight gain, which may explain the relationship between chronotype and cardiometabolic parameters.

In this study, a comprehensive dataset was created to investigate the relationship between chronotype and CVD risk in patients with BD. The data include a variety of potentially influential factors such as clinical data, exercise habits, eating attitudes and sleep quality. Studies focusing on CVD, one of the leading causes of death in BD patients, are limited. To our knowledge, our study is the first in the literature to examine all these areas together.

The limitations of our study include its cross-sectional design, which restricts the ability to establish cause-effect relationships, and the absence of a separate analysis for patients taking psychotropic drugs, who are at higher risk of metabolic disease, or a study on the side effects of these drugs. Additionally, our study is limited by the fact that we did not inquire about participants' eating habits and did not calculate their calorie intake.

Further comprehensive studies are needed to more clearly delineate the relationship between sleep, chronotype characteristics and CVD in people diagnosed with BD, and to clarify the direction of the underlying causality. These studies should consider various confounding factors, such as demographic differences, details of exercise habits, concomitant depressive symptoms, metabolic and circadian effects of treatments, differences in social rhythm and lifestyle, and genetic factors, compared with healthy controls.

CONCLUSION

Based on the current study, individuals with an evening chronotype had poorer sleep quality, unhealthier eating habits, high risk of CVD, and higher prevalence of MetS. For patients diagnosed with BD, there is agreement that chronobiological treatments and interventions designed to align with endogenous circadian and social rhythms could help improve affective

symptoms and sleep quality. This may have implications for both the clinical course of BD and the prevention of associated cardiometabolic diseases. Further research into chronotype could provide valuable insights into the identification and treatment of those at higher risk from both a psychological and cardiometabolic perspective.

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Original Research

Evaluation of the Pons, Midbrain, Thalamus, Hippocampus, and Trigeminal Nerve with MRI in Patients with Cluster Headache

Mehmet Hamdi Şahan [1], Nuray Bayar Muluk [2,*], Fatih Koçtürk [3]

[1] Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
[2] Department of ENT, Faculty of Medicine, Kırıkkale University, Kırıkkale, Türkiye
[3] Department of Neurology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye

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Corresponding Author
Nuray Bayar Muluk, MD
Address: Department of ENT, Faculty of Medicine, Kırıkkale University, Kırıkkale, Türkiye
E-mail: nuray.bayar@yahoo.com; nurayb@hotmail.com

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ABSTRACT

Objectives: We investigated the volumetric changes of the brain structures and trigeminal nerve diameters in cluster headache (CH) by cranial MRI.

Methods: The cranial MRI images of 30 adult patients with CH and 30 adult subjects with normal cranial MRI results were included. In both groups, pons, midbrain, thalamus, and hippocampus volumes; and trigeminal nerve diameters were measured.

Results: There were no significant differences between pons (p=0.849), midbrain (p=0.855), bithalamic ($p=0.553^{Right}$, $p=0.523^{Left}$), and hippocampus volumes ($p=0.930^{Right}$, $p=0.698^{Left}$). In CH group, trigeminal nerve diameter (2.38±0.47 mm) was non-significantly higher than the control group (2.29±0.44 mm) (p=0.131). In the CH group, left thalamus and right hippocampus volumes were significantly higher than the contralateral side ($p<0.05$). In CH group, there were positive correlations between the pons and thalamus ($p=0.037^{Right}$ and $p=0.037^{Left}$) and hippocampus volumes ($p=0.002^{Right}$, $p=0.005^{Left}$); midbrain and bithalamic volumes ($p=0.001^{Right}$, $p=0.001^{Left}$); and right trigeminal nerve diameter (p=0.029); thalamus and pons($p=0.037^{Right}$, $p=0.037^{Left}$); and midbrain volumes ($p=0.001^{Right}$, $p=0.001^{Left}$); right and left hippocampus volumes (p=0.000); right and left trigeminal nerve diameters (p=0.000). In females, right hippocampus volumes were smaller than those in males (r= -0.374, p=0.042).

Conclusion: In CH patients, left thalamus volume was higher; and left hippocampus volume was lower. In CH patients, the limbic system and especially left hippocampus may be affected and get lower in volumetric analysis. Additionally, the right thalamus is affected showing lower volume in CH patients.

Keywords: cluster headache, pons, midbrain, thalamus, hippocampus, trigeminal nerve.

INTRODUCTION

Cluster headaches (CH) are primary headache disorders and are considered disorders of the brain [1,2]. In CH, ipsilateral hypothalamic gray area activation occurs, however in migraine without aura, the contralateral side of the brainstem activation was present [3-5]. There are other neurological symptoms, such as sensory, homeostatic, autonomic, cognitive and emotional processes that can be related to headaches. These symptoms are

related to the modulation of specific brainstem nuclei [1].

CH patients have severe or very severe and unilateral attacks of pain ("orbital, supraorbital or temporal "). Attacks last 15-180 minutes and occur from one to 8 times a day. İpsilateral conjunctival injection, nasal congestion, lacrimation, rhinorrhea, myosis, ptosis or eyelid edema, forehead and facial sweating are associated with the attacks; and one or more of these symptoms are seen [6]. CH may be episodic or chronic. In episodic form, "at least 2 cluster phases lasting 7 days to 1 year are separated by painless periods lasting at least 3 months"; and in chronic form, "clusters occur for a year or more without remission or occur with remission lasting less than 3 months" [6].

In the central and peripheral nervous system, various structures are involved in CH attack generation. These are "trigeminovascular system, parasympathetic nerve fibers (trigeminal autonomic) reflex and hypothalamus". When all of these structures are involved, CH attacks are initiated; and later, processing and perception of pain cortical areas of CNS will be activated [7]. Hypothalamus has an important role in the pathophysiology of the facial pain syndromes, including CH [8].

In the present study, we investigated the volumetric changes of the brain structures (pons, midbrain, thalamus, hippocampus) in CH patients; and the trigeminal nerve was also evaluated by cranial MRI

MATERIAL AND METHODS

This retrospective study was conducted at Gaziantep University, Medical Faculty, Radiology and Neurology Departments and Kırıkkale University, Medical Faculty, Department of Otolaryngology. This study was approved by "Gaziantep University Clinical Researches Ethics Committee" (Decision Number: 2022/303, Date:28.09.2022) and conducted according to the Declaration of Helsinki.

Main Points

- Hippocampus is located in the limbic system
- The left hippocampus may be affected and get lower in volumetric analysis in CH patients
- The right thalamus is affected showing lower volume in CH patients

Study Population and Exclusion Criteria

Patients diagnosed with cluster headache (CH) from our neurology clinic and a control group with similar demographic characteristics who underwent cranial MRI for any reason and met the study criteria were analyzed. A total of 60 cranial MRI sections were included, including 30 patients with cluster headaches and 30 control group subjects, taking into account similar studies in the literature [9,10]. Cluster headache patients were over 18 years of age, and diagnosed with a new episodes of cluster headache according to the criteria of the "International Classification of Headache Disorders (ICHD-3)" [11-13]. The mean ages of the CH group were 35.27±8.15 years (ranging from 19 to 53 years).

The control group consisted of subjects who had retrospective cranial MRI examinations for any reason, met the exclusion criteria, and matched the same demographic characteristics as the cluster headache group. Both groups included those who had complete and appropriate cranial MRI images based on measurement parameters. The mean ages of the control group were 35.20±7.51 years (ranging from 20 to 47 years).

Similar studies in the literature were evaluated [1,14]; and the minimum number of individuals required to determine the statistically significant volume change between the groups was found to be 52 in total, with 26 in each group (α=0.05, 1-β=0.80), to conduct statistical analysis using Gpower3.1 version.

Exclusion Criteria

Those with a history of cranial trauma and surgery, intracranial masses, diabetes or any metabolic disease, demyelinating or degenerative diseases affecting cerebral structures, "previous medical or neurological history", those taking any neurological drugs or substances, and those with "congenital and anatomical variations in the brain" were not included in the study.

MRI Technique and Measurements

MRI scans were conducted using a "3.0 Tesla MRI system" ("Ingenia, Philips Healthcare, Best, Netherlands") with a cranial coil. At Gaziantep University Hospital, the standard cranial MRI protocol for the 3.0-T MRI system included the following: T1-FFE (Fast Field Echo) sequences were performed in the "sagittal and axial planes" with parameters of TR ms/TE ms; 330/20, a field of view (FOV) of 230x130 mm, and a matrix of 256 × 139 mm. These scans had "a slice thickness of 4 mm and an intersection gap of 0.5 mm", resulting in 30-32 sagittal

and axial slices. T2-TSE ("Turbo Spin Echo") sequences were performed in the coronal plane with parameters of "TR ms/TE ms; 4040/80", a "FOV of 200x152 mm", and a matrix of 288 × 163 mm. These images had a "slice thickness of 4 mm" and "an intersection gap of 0.5 mm", resulting in 34 coronal slices.

Following image processing at the workstation, measurements were carried out by a radiologist manually (MHŞ).

Pons Volume (cm^3): The pons area was measured in each section from the axial T1-weighted images. The total volume was calculated by summing these areas and multiplying by the combined section thickness and intersection gap [7,15,16] (refer to Figure 1A, B).

Midbrain Volume (cm^3): Similarly, the midbrain area was measured from the axial T1-weighted images. The volume was determined by summing these areas and multiplying by the total section thickness and intersection gap [1,15] (refer to Figure 2A, B).

Bithalamic Volume (cm^3): For the bithalamic volume, the areas of the right and left thalami were measured from the axial T1-weighted images. The total volume was calculated by summing these areas and multiplying by the combined section thickness and intersection gap [1,15] (refer to Figure 3A, B).

-Hippocampus volumes (cm^3): After measuring the hippocampus areas in each section from coronal T2 weighted images, the sum of the areas was calculated. The volume was obtained by "multiplying this calculated value" by "the sum of the section thickness with the intersection gap" [1,14-18] (Figure 4A, B).

-Trigeminal nerve diameters (mm): The diameters of the trigeminal nerve was measured from the coronal T2 weighted images, in the cisternal region where the trigeminal nerve emerges from the pons, where it is most clearly seen [19-22] (Figure 5).

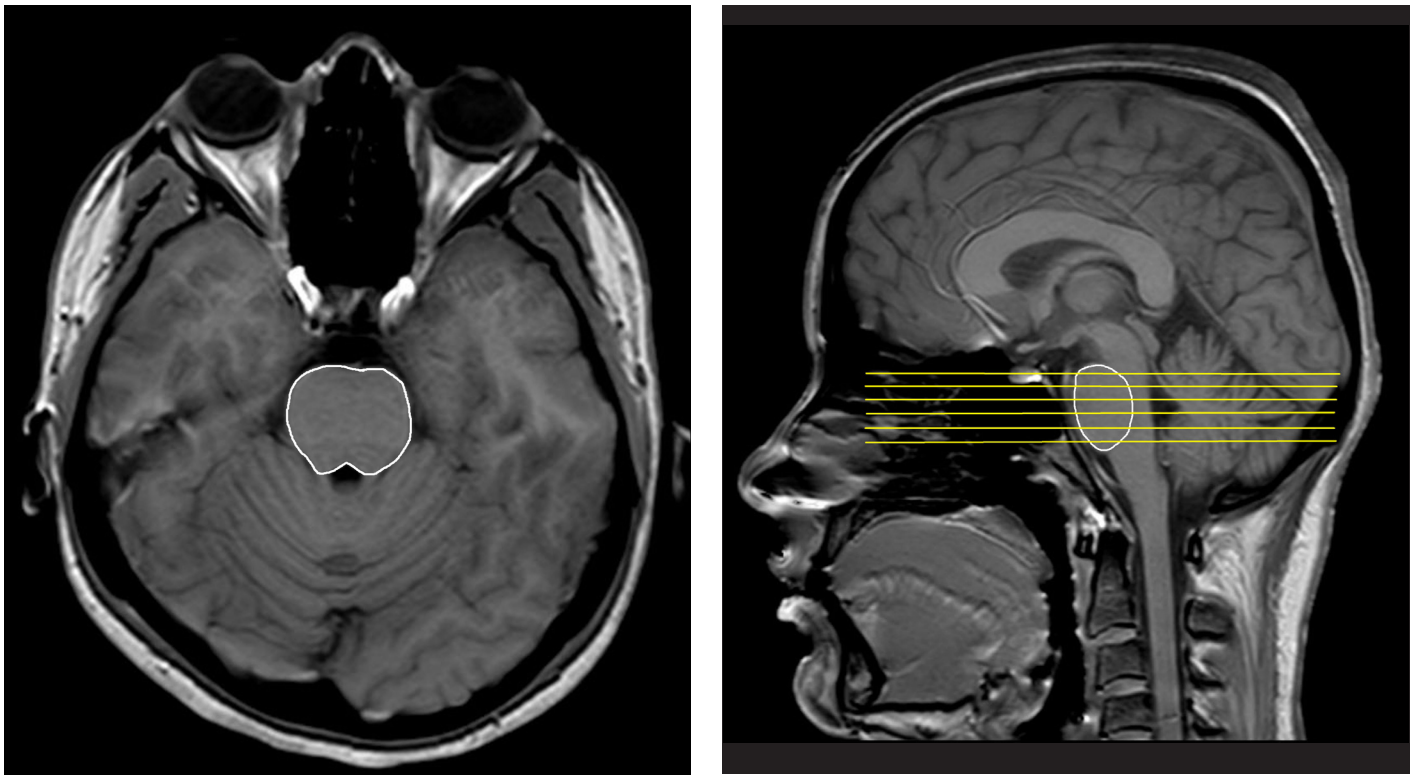


Figure 1. **A-** Measurement of the pons area in axial T1W images, **B-** Sections passing through the pons in sagittal T1W images.

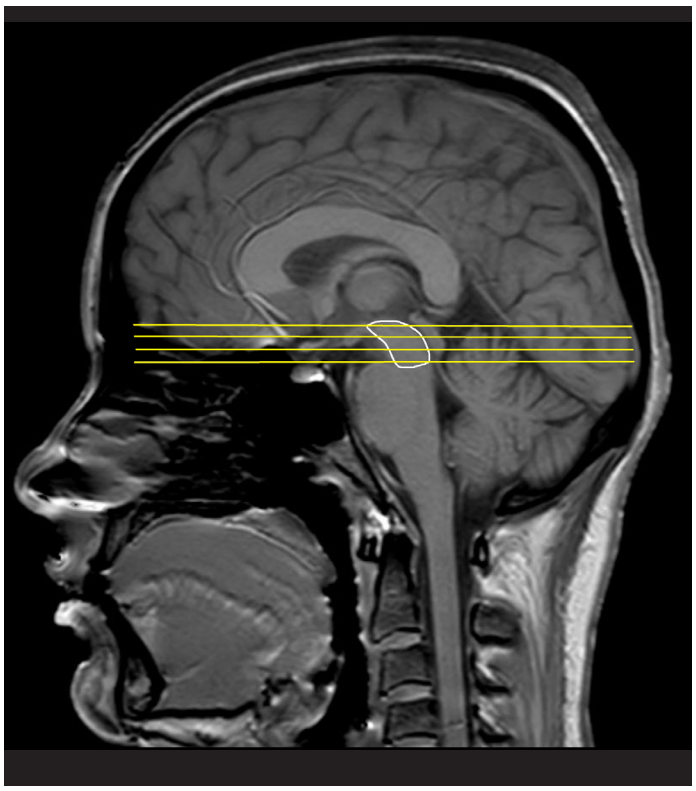


Figure 2. A- Measurement of the midbrain area in axial T1W images,

B- Sections passing through the midbrain in sagittal T1W images

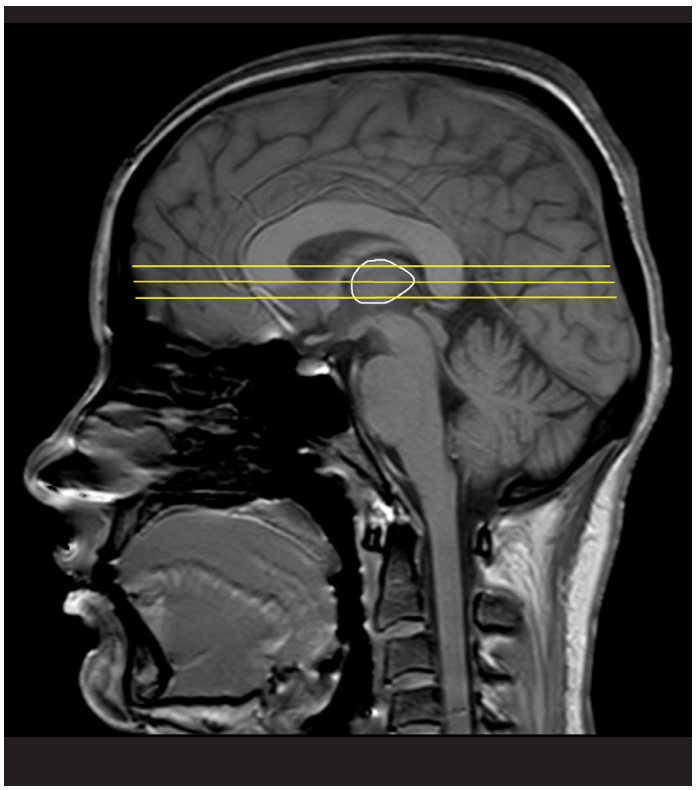
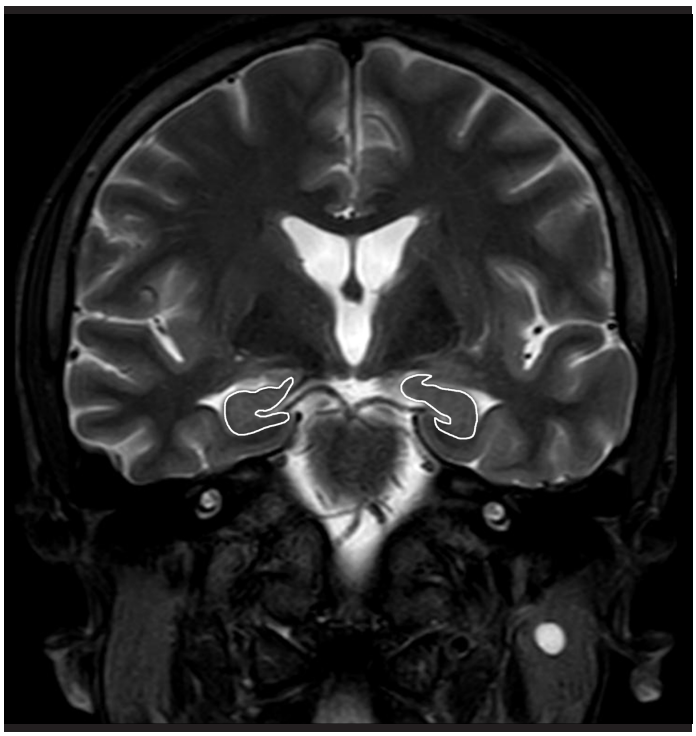


Figure 3. A- Measurement of bilateral thalamus area in axial T1W images,

B- Sections passing through the thalamus in sagittal T1W images.



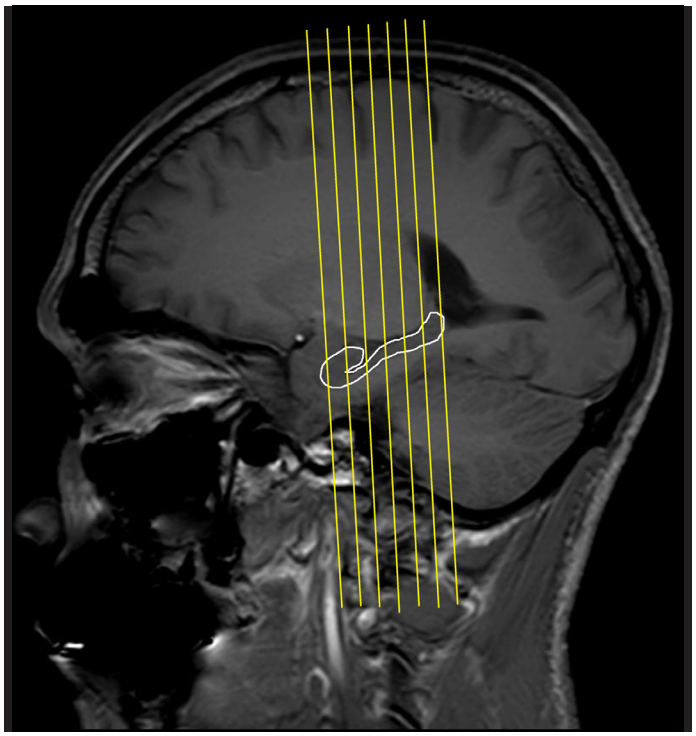


Figure 4.A-Measurement of bilateral hippocampus area in coronal T2W images,

B- Sections passing through the hippocampus in sagittal T1W images.

Figure 5. The appearance of both trigeminal nerve in coronal T2W images (white arrows), measurement technique in magnified images.

Statistical Analysis

Data analysis for this study was performed using SPSS for Windows version 21.0 ("SPSS, INC, an IBM Company, Chicago, Illinois"). Initially, the Kolmogorov-Smirnov test was applied. Non-parametric tests were conducted if the p-value was < 0.05, while parametric tests were used if the p-value was > 0.05. The statistical methods employed included the "Chi-square test, independent samples t-test, paired samples t-test, Pearson correlation, and Spearman's rank correlation coefficient". A p-value of less than 0.05 was deemed statistically significant.

RESULTS

In the cluster headache (CH) group, there were 13 males (43.3%) and 17 females (56.7%). The control group comprised 12 males (40.0%) and 18 females (60.0%), with no significant gender distribution differences between the two groups ($p=0.793$, $\chi2=0.069$). Age differences between the groups were not significant ($p>0.05$) (Table 1).

Pons, Midbrain, Bithalamic, and Hippocampus Volumes

Measurements for pons, midbrain, bithalamic, and hippocampus volumes in both the CH and control groups are shown in Table 1 and Figure 6.

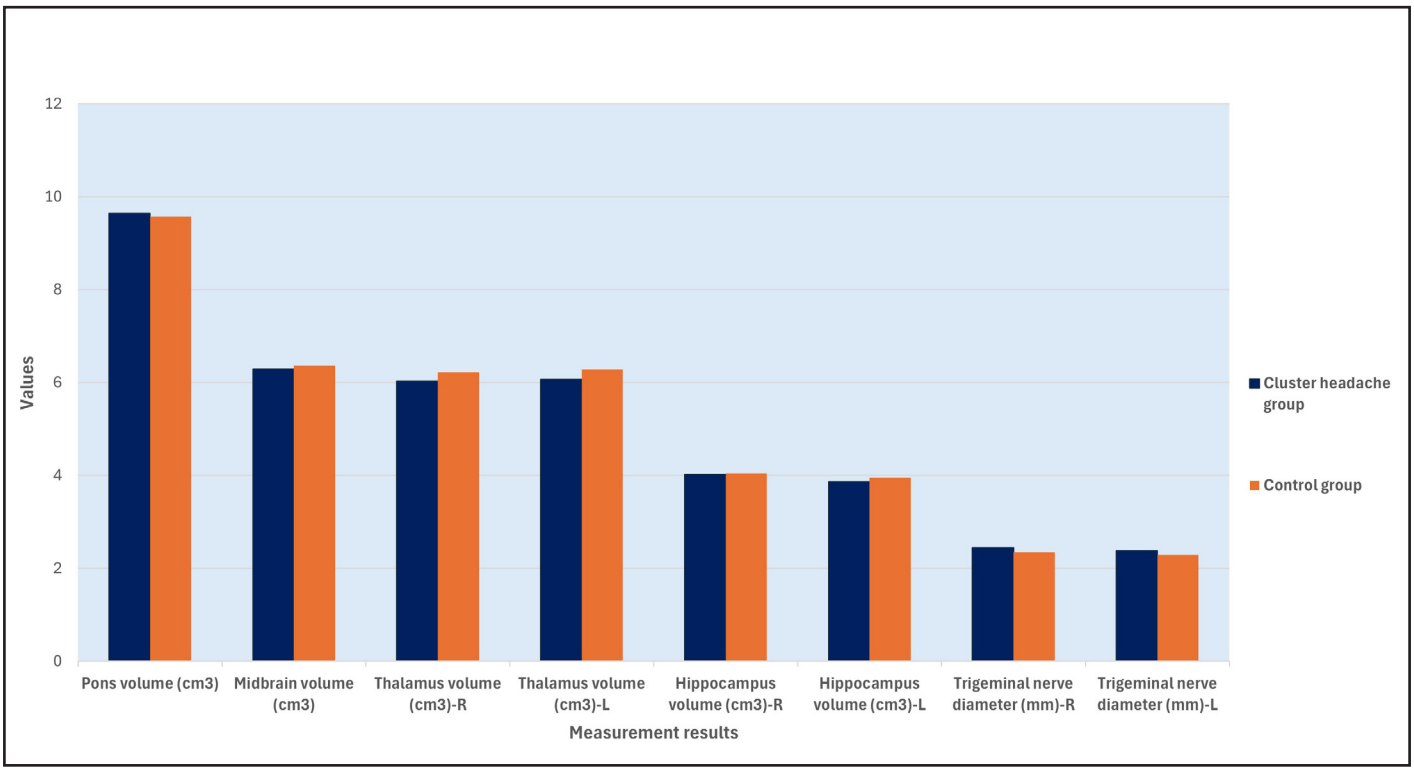


Figure 6. Measurement results for pons, midbrain, bithalamic, and hippocampus volumes in both the CH and control groups

Table 1. Measurement results in the cluster headache and control groups

		Group 1 (Cluster headache) (n=30)			Group 2 (Control group) (n=30)			P*
		Median	Std.Dev.	Mean	Median	Std.Dev.	Mean	
Age		35.27	37.00	8.15	35.20	36.00	7.51	0.974
Measurement results								
Pons volume (cm^3)		9.64	9.70	1.64	9.57	9.20	1.46	0.849
Midbrain volume (cm^3)		6.29	6.27	1.40	6.36	6.05	1.39	0.855
Thalamus volume (cm^3)	R	6.03	5.63	1.33	6.22	5.93	1.07	0.553
	L	6.07	5.70	1.35	6.28	6.12	1.11	0.523
	P**	0.027			0.124			
Hippocampus volume (cm^3)	R	4.02	3.97	0.68	4.04	4.25	0.88	0.930
	L	3.87	3.75	0.66	3.95	4.15	0.86	0.698
	P**	0.019			0.045			
Trigeminal nerve diameter (mm)	R	2.45	2.45	0.54	2.34	2.30	0.46	0.407
	L	2.38	2.42	0.47	2.29	2.31	0.44	0.447
	P**	0.131			0.273			

*p value shows the results of independent samples t-test

**p value shows the results of paired samples t-test

Table 2. Correlation test results in the cluster headache group

			Pons Volume (cm^3)	Midbrain volume (cm^3)	Thalamus volume (cm^3)		Hippocampus volume (cm^3)		Trigeminal nerve diameter (mm)	
			R	L	R	L	R	L		
Pons volume (cm^3)		r		0.124	0.382	0.383	0.549	0.501	0.064	0.132
		P*		0.515	0.037	0.037	0.002	0.005	0.735	0.487
Midbrain volume (cm^3)		r	0.124		0.582	0.588	-0.016	-0.022	0.399	0.355
		P*	0.515		0.001	0.001	0.933	0.909	0.029	0.054
Thalamus volume (cm^3)	R	r	0.382	0.582		0.998	0.266	0.212	0.246	0.273
		P*	0.037	0.001		0.000	0.155	0.260	0.191	0.144
	L	r	0.383	0.588	0.998		0.277	0.217	0.258	0.277
		P*	0.037	0.001	0.000		0.138	0.249	0.168	0.138
Hippocampus volume (cm^3)	R	r	0.549	-0.016	0.266	0.277		0.878	0.190	0.176
		P*	0.002	0.933	0.155	0.138		0.000	0.316	0.352
	L	r	0.501	-0.022	0.212	0.217	0.878		0.168	0.191
		P*	0.005	0.909	0.260	0.249	0.000		0.375	0.312
Trigeminal nerve diameter (mm)	R	r	0.064	0.399	0.246	0.258	0.190	0.168		0.879
		P*	0.735	0.029	0.191	0.168	0.316	0.375		0.000
	L	r	0.132	0.355	0.273	0.277	0.176	0.191	0.879	
		P*	0.487	0.054	0.144	0.138	0.352	0.312	0.000	
Age		r	0.061	0.196	0.018	0.032	-0.096	-0.203	-0.025	-0.066
		P*	0.747	0.299	0.924	0.866	0.613	0.281	0.896	0.730
Gender (Code 1: Male, Code 2: Female)		r	-0.058	-0.214	-0.222	-0.229	-0.374	-0.265	-0.238	-0.070
		P**	0.759	0.256	0.238	0.223	0.042	0.158	0.206	0.713

* p value shows the results of Pearson correlation test

** p value shows the results of Spearman's correlation rho efficient test

No significant differences were found between the pons (p=0.849), midbrain (p=0.855), bithalamic ($p=0.553^{Right}$, $p=0.523^{Left}$), and hippocampus volumes ($p=0.930^{Right}$, $p=0.698^{Left}$) of the CH and control groups. Within the CH group, the volume of the left thalamus was notably greater than that of the right thalamus (p=0.027) (see Table 1). In both the CH (p=0.019) and control (p=0.045) groups, the right hippocampus volume was significantly larger compared to the left hippocampus volume (Table 1).

Trigeminal Nerve Diameters

Trigeminal nerve diameters did not show significant differences between the CH and control groups ($p=0.407^{Right}$, $p=0.447^{Left}$). Moreover, there were no significant differences in the diameters of the right and left trigeminal nerves within either group (Table 1).

Correlation Test Results in CH Group

Correlation analysis results for the CH group are provided in Table 2.

In the CH group, left thalamus and right hippocampus volumes were significantly higher than the contralateral side ($p<0.05$). In CH group, there were positive correlations between the pons and thalamus ($p=0.037^{Right}$ and $p=0.037^{Left}$) and hippocampus

volumes ($p=0.002^{Right}$, $p=0.005^{Left}$); midbrain and bithalamic volumes ($p=0.001^{Right}$, $p=0.001^{Left}$); and right trigeminal nerve diameter (p=0.029); thalamus and pons($p=0.037^{Right}$, $p=0.037^{Left}$); and midbrain volumes ($p=0.001^{Right}$, $p=0.001^{Left}$); right and left hippocampus volumes (p=0.000); right and left trigeminal nerve diameters (p=0.000). In females, right hippocampus volumes were smaller than those in males (r= -0.374, p=0.042) (Table 2).

DISCUSSION

CH is a primary headache disorder marked by intense, unilateral pain and accompanying "ipsilateral autonomic symptoms", falling under the category of trigeminal autonomic cephalalgias. It includes conditions such as "paroxysmal hemicrania, acute unilateral neuralgic headaches, and hemicranial continua", all contributing to the "trigeminal autonomic cephalalgia spectrum" [23]. CH affects less than 1% of the population and is more commonly observed in men [24,25]. The onset typically occurs between the ages of 20 and 40 years [24,25].

Several factors can trigger CH attacks. For instance, "subcutaneous histamine injections" induce attacks in 69% of patients. Other potential triggers include "seasonal changes, allergens, stress, or nitroglycerin". Alcohol may provoke attacks during a cluster period but not during remission. Approximately 50% of patients consume alcohol, and "80%" are heavy smokers [6]. Vascular changes, such as "extracranial temporal artery dilation" following the onset of pain, may be secondary to primary neuronal discharge [6].

Our findings indicated no significant differences in the volumes of the "pons, midbrain, bithalamic regions, or hippocampus" between the CH and control groups. Although there were no significant differences in trigeminal nerve diameters between the CH and control groups, the CH group exhibited a slightly larger average diameter (2.38±0.47 mm) compared to the control group (2.29±0.44 mm). A larger sample size might reveal more significant differences. In the CH group, female subjects had smaller right hippocampus volumes compared to males.

The exact pathophysiology of CH remains unclear (26,27). The cyclical nature of attacks suggests a disruption in biological rhythms, potentially involving central disinhibition of "nociceptive and autonomic pathways", especially within the trigeminal system controlled by the hypothalamus [28]. Our study's observation of a slightly increased trigeminal nerve diameter in CH patients may indicate an influence on the trigeminal pathways.

Cluster headaches typically follow a circadian and seasonal pattern, with frequent night-time attacks. This pattern suggests a significant role of the hypothalamus in the condition's pathophysiology. The daily attack cycle tends to last about an hour in men, indicating possible "gender-specific functional differences" in the hypothalamus [7,29].

Lee, et al [30] compared the "limbic structures" and covariance network in CH patients and healthy controls. Volumetric analysis of the "subcortical limbic structures" ("the hippocampus, amygdala, thalamus, mammillary body, hypothalamus, basal forebrain, septal nuclei, fornix, and nucleus accumbens") was performed. Patients with cluster headaches showed significant alterations in the "limbic covariance network". They found that the left hippocampus volume of the CH patients was lower than the control group [30]. In the present study, no significant differences were detected between hippocampus volumes of the CH and control group. However, in the CH group, the left hippocampus volume was significantly lower than the right hippocampus volume.

"Functional imaging with PET" shows ipsilateral hypothalamus activation during CH attacks [23]. Long-term "high-frequency electrical stimulation of the posterior hypothalamus with an implanted electrode" may relieve the symptoms of this disorder [4,31,32].

In the MRI-diffusion study of Király et al. [33], the size of subcortical structures ("caudate, putamen, and thalamus") and diffusion parameters were normal in controls. However "right amygdala's mean fractional anisotropy, right caudate nucleus' mean axial diffusivity parallel (AD) and diffusion values, and right pallidum's radial diffusion (RD) were higher in CH patients. The mean anisotropy of the right pallidum was lower in the CH group. Positive correlations were observed between left and right hippocampus volumes, as well as negative correlations between headache days and certain brain metrics such as AD values of the thalamus and mean diffusivity and RD values of the left hippocampus [33]. In the present study, the volume of the left thalamus was significantly greater compared to the right, while the volume of the left hippocampus was notably smaller than the right. Additionally, positive correlations were observed between the volumes of the pons, thalamus, and hippocampus; between the midbrain, bithalamic volumes, and the right

trigeminal nerve diameter; and between the volumes of the right and left hippocampus. These findings are consistent with those reported by Király et al. [33].

PET studies [3] have shown activation in the "ipsilateral inferior hypothalamic gray matter" during CH attacks, with "voxel-based morphometry" revealing structural abnormalities in this area [34]. Other research suggests that trigeminal nerve stimulation does not directly activate the hypothalamus [35], which supports the hypothesis that the hypothalamus plays a causative role in CH [7]. Dysfunctional interactions between pain matrix brain regions may lead to disinhibition of the "hypothalamic-trigeminal pathway", triggering CH attacks. Ipsilateral parasympathetic symptoms might be due to direct hypothalamic effects or peripheral stimulation via "the superior salivatory nucleus (SSN) parasympathetic efferents" [36,37].

Limitations

The limitations of our work are listed as the followings: (1) The most important limitation in our study is that we have performed manual volumetric analysis; and did not evaluate inter/intra-observer variability. To reduce this limitation, extensive studies have been conducted using empirical guidelines for determining anatomical boundaries. Automated volumetric analysis tools can be used in the future studies. (2) Lack of standardization in the measurements and the absence of normative data that would allow the physician to interpret bio-benchmark values in patient care. (3) Since the study is retrospective, the MRI sections include routine cranial MRI slices. It does not include sections with different MRI sequences specific to measurements.

CONCLUSION

As a conclusion, in CH patients left thalamus volume was higher; and left hippocampus volume was lower compared to the other side. No differences were found compared to the control group. There were positive correlations between pons, thalamus, midbrain and hippocampus volumes; and trigeminal nerve diameters. In CH patients, the limbic system and especially the left hippocampus may be affected and get lower in volumetric analysis. Additionally, the right thalamus is affected showing lower volume in CH patients.

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Informed Consent: There is no need to take informed consent because the data were evaluated retrospectively.

Ethical Approval: This study is retrospective. Ethics committee approval was obtained from Gaziantep University Clinical Researches Ethics Committee Decision Number: 2022/303, Date:28.09.2022).

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Original Research

An Assessment of the Relationship Between the Beck Anxiety Inventory and Stress Hormones Among Intern Doctors in the Emergency Department

Süleyman Nogay[1], Mustafa Sabak[1], Cuma Yıldırım[1]

[1] Department of Emergency Medicine, Gaziantep University School of Medicine, Gaziantep, Türkiye

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Corresponding Author
Mustafa Sabak, MD
Address: Gaziantep University Faculty of Medicine Emergency Department Gaziantep, Türkiye
E-mail: mustafasabak@hotmail.com

ABSTRACT

Objective: We aimed to investigate the anxiety effect of working conditions on intern doctors in emergency department (ED), the severity of this effect according to the Beck Anxiety Inventory (BAI), and the hormonal factors involved in the etiology of anxiety.

Methods: A prospective analysis was conducted on a group of 74 intern doctors who completed training in the ED between May and October 2017. Participants were asked to complete the BAI form and have their blood samples taken at 07:00 a.m. during both the first and last night shifts. The blood samples have been utilized in the study of Adrenocorticotropic Hormone (ACTH), Atrial Natriuretic Peptide (ANP) and Cholecystokinin (CCK), hormones that have been found to have a strong correlation with stress levels. A comparison of hormone levels and BAI scores was conducted before and after the internship to assess any changes.

Results: The sample size for the study consisted of seventy-four interns, of which 47.3% (n=35) were identified as male. The average age was 25 +/- 2 years. No significant difference was detected in ACTH levels before and after the internship (p = 0.087), although the end-of-internship BAI score and ANP and CCK levels were found to be significantly higher in the entire group (p=0.001, p=0.001, p=0.048; respectively). While the post-internship BAI score and ANP levels were significantly higher in males (p=0.001, p=0.015, respectively), no significant difference was detected in the ACTH and CCK levels before and after the internship (p=0.128, p=0.077, respectively). While post-internship BAI score, ACTH and ANP levels were found to be significantly higher in female (p=0.001, p=0.026, p=0.001; respectively); No significant difference was detected in CCK levels (p = 0.155).

Conclusion: Emergency departments are places where stress and anxiety are intensely experienced. The post-internship hormone levels reveal a predominantly anxiolytic pattern (with no notable alteration in ACTH levels but a rise in ANP), while the elevated BAI score can be attributed to the subjective nature of this assessment tool. Identifying the hormones that increase or decrease in response to stress and conducting further research on treatment may be one method of coping with stress.

Keywords: Emergency Medicine, Intern Doctor, Stress, Anxiety, Beck Anxiety Inventory, Stress Hormones

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INTRODUCTION

Stress refers to the body's response, both psychological and physical, to adapt to external stimuli, whether physical or psychological in nature [1,2]. Prolonged exposure to stress has been associated with the onset of multiple physiological and psychological disorders, such as depression, anxiety disorders, disordered sleep patterns, cardiovascular problems, and cancer. It has been observed that this matter can lead to manifestations such as ambivalence, self-distrust, worthlessness, pessimism, and intense outrage. Developing stress coping skills, especially at a young age, will be crucial in preventing many diseases [3,4]. The emotions of fear, worry, and curiosity can all be classified as anxiety. In broad scope, it may be described as a state of despondency and disquietude stemming from the dread or anticipation of calamity in the midst of a perilous circumstance [3,5]. Studies indicate that anxiety disorders are a frequent occurrence in children and teenagers [3,6]. It is of utmost importance to mention that issues pertaining to the department and security are prominent contributors to the heightened levels of anxiety observed in students [1,7].

Adrenocorticotropic Hormone (ACTH) is one of the most important stress hormones. It stimulates the synthesis of cortisol in the adrenal cortex [8]. Cortisol is a corticosteroid hormone and is secreted in response to stress. Serum cortisol level can vary depending on ACTH level, emotional stress and physiological stress sources (hypoglycemia, disease, fever, acute trauma, surgery, fear, pain, physical strain, etc.) [9,10]. Cholecystokinin (CCK) is a neuropeptide with strong anxiety-inducing properties, and it is commonly present in the central nervous system, particularly in the limbic system. It acts through CCK-A and CCK-B receptors. Even though CCK-A has a stronger influence on anxiety, CCK-B is considered to have a role in panic disorder [10-12]. Atrial Natriuretic Peptide (ANP) is widely found in atrial cells and is a peptide hormone released in response to atrial stretch [13]. It causes diuresis and natriuresis [13]. ANP is widely found in the body outside the atrium and is known to function as a neuropeptide in the nervous system [10,12]. In general, ANP suppresses the hypothalamo-pituitary-adrenal (HPA) system at almost every stage during stressful conditions. However, it has been suggested that ANP is not a general inhibitor of the HPA system, but a complex anti-stress mechanism that operates through the emotional aspects of stress [10,14].

Main Points

- The health of emergency workers is greatly impacted by stress and anxiety.
- The function of CCK in stress and anxiety remains uncertain, despite the known roles of ACTH and ANP in these conditions.
- Studies are needed to develop methods to deal with stress in emergency services.

The Beck Anxiety Scale (BAI) is a validated psychological test of the Likert type, commonly used internationally to measure anxiety severity and assess the frequency of anxiety symptoms [15,16].

The main goal of our investigation is to advance the current methods of stress management by analyzing the levels of anxiety and stress hormones in newly appointed intern doctors within the emergency setting.

MATERIALS AND METHODS

Study Design and Setting

The study was conducted prospectively at Gaziantep University Şahinbey Research and Application Hospital Emergency Department (ED) between 1 May 2017 and 31 October 2017.

Selection of participants

A total of 74 intern doctors, consisting of 9 groups, who worked as physician candidates in the ED for 2-month periods between these dates, and were included in the research. A pregnant woman and two male intern doctors receiving psychiatric treatment were not included in the study. Six Intern doctors refused to participate in the study.

Inclusion Criteria of the Research

- Be a volunteer,
- To be in a state of complete mental and physical well-being,
- As a physician candidate, working in the ED at Gaziantep University Şahinbey Research and Application Hospital.
-

Exclusion Criteria of the Research

- To refuse being a volunteer.
- Condition of being pregnant or potentially pregnant
- Having a disease that affects ACTH and cortisol levels, such as a pituitary gland tumor or adrenal gland tumor, or using medication that affects ACTH and cortisol levels,

- Having a disease that affects the ANP level, such as chronic renal failure, congestive heart failure, or using medication that affects the ANP level,
- Having a gastrointestinal system disease that will affect the CCK level or using medication that will affect the CCK level,
- Having a psychiatric illness such as severe anxiety disorder, active psychosis, or major depression,
- Using medications such as steroid, anxiolytic, sedative
- Having hormonal dysfunction.
- Having recently experienced any mental or physical trauma (death of a close relative, traffic accident, divorce, etc.) that may lead to emotional depression.

Method of Data Collection

A four cc blood sample was taken from the antecubital region of the arm that the person does not actively use, either right or left, around 07:00 in the morning during the night shifts, corresponding to the start and completion period of the ED internship. Two cc were equally distributed between the hemogram and biochemistry tubes. The blood in the tubes was centrifuged at 4000 rpm for 10 minutes and separated it into plasma and serum components, respectively. After the serum and plasma samples were placed in separate Eppendorf tubes and recorded, they were stored in the deep freezer at -80 oC in the Basic Medical Sciences Biochemistry Laboratory of Gaziantep University Faculty of Medicine until the study date.

Before and after the internship, intern doctors were asked to fill out the BAI simultaneously while blood samples were taken.

Measurements

ACTH was studied from plasma samples obtained by centrifuging blood in hemogram tubes. CCK and ANP were studied from serum samples obtained by centrifugation of blood in biochemistry tubes.

Plasma samples were taken from the deep freezer and allowed to reach to room temperature.

ACTH levels in plasma samples were measured using a human ELISA kit (SunRed, PRC). This examination works with the immunoassay competitive enzyme inhibition technique.

Serum samples were taken from the deep freezer and then allowed to reach to room temperature.

ANP levels in serum samples were measured using the human ELISA kit (SunRed, PRC). This kit utilizes the double antibody sandwich ELISA technique to quantify ANP serum levels.

CCK levels in plasma samples were measured using the human ELISA kit (SunRed, PRC). This examination works with the immunoassay competitive enzyme inhibition technique.

Definitions

The Beck Anxiety Inventory is a self-assessment scale with 21 items, and each item is scored between 0 and 3. Patients' anxiety levels are determined by the scores obtained from the scale. 0–7 points indicate low levels of anxiety, 8–15 points suggest mild anxiety, 16–25 points indicate medium anxiety, and 26–63 points indicate high levels of anxiety [15]. For blood parameters (e.g. CCK) and BAI, 'first' refers to the pre-internship values, and 'last' refers to the post-internship values.

Statistics

The statistical analysis was conducted using the SPSS 22.0 software package. The normal distribution suitability of numerical data was tested using the Shapiro-Wilk test. The Mann Whitney U test was used to compare variables that did not show normal distribution in two groups, and the Kruskel Wallis test was used to compare them in more than two groups. A Paired T test was used to compare normally distributed dependent variables, and a Wilcoxon test was used to compare non-normally distributed dependent variables. All data were expressed as mean ± standard deviation, and a P value of <0.05 was considered statistically significant.

RESULTS

A total of 74 intern doctors, 47.3% of whom (n=35) were male, were included in the study. The average age was 25+/- 2 years.
At the end of the internship, Beck Anxiety Inventory scores were significantly higher in intern doctors (p=0.001).

No significant difference was detected between ACTH levels before and after the internship among the participants (p = 0.087). However, ANP and CCK levels were found to be significantly higher at the end of the internship (p = 0.001 and p = 0.048, respectively).

No significant difference was detected between the ACTH and CCK levels of male intern doctors before and after the internship (p=0.128 and p=0.077; respectively). However, ANP levels

were found to be significantly higher at the end of the internship (p=0.015).

ACTH and ANP levels of female intern doctors were found to be significantly higher at the end of the internship (p=0.026 and p=0.001; respectively), but no significant difference was detected between CCK levels before and after the internship (p=0.155). The pre-internship BAI scores of women were significantly higher than those of men (p=0.048). No significant difference was detected between genders in BAI scores after internship (p=0.124) (Table 1).

No significant difference was found in the pre-internship levels of ACTH, ANP, and CCK between genders (p=0.713 and p=0.066; p=0.110; respectively) (Table 2).

There was no significant difference in ACTH, ANP, and CCK levels between the genders after the internship (p=0.176, p=0.063 and p=0.141, respectively) (Table 3).

Table 1. The distribution of pre and post-internship Beck Anxiety Inventory scores by gender.

Beck Anxiety Inventory	Gender	N	Mean (pg/ml)	P*
Pre-Internship	Male	35	7,57 ± 8,06	0,048
	Female	39	10,05 ± 7,26	
Post Internship	Male	35	13,40 ± 9,52	0,124
	Female	39	15,71 ± 7,80	

**P<0,05 significant.*

Table 2. Distribution of Pre-Internship ACTH, ANP and CCK Levels among Gender

Hormone	Gender	N	Mean (pg/ml)	P*
CCK	Male	35	623,62 ± 136,82	0,110
	Female	39	572,99 ± 139,09	
ANP	Male	35	1939,87 ± 1086,69	0,066
	Female	39	2339,78 ± 737,85	
ACTH	Male	35	1695,98 ± 2442,03	0,713
	Female	39	2701,30 ± 4614,46	

**P<0,05 significant. CCK: Cholecystokinin; ANP: Atrial natriüretik peptid; ACTH: Adrenocorticotropic Hormone*

Tablo 3. Distribution of Post-Internship ACTH, ANP and CCK Levels among Gender

Hormone	Gender	N	Mean (pg/ml)	P*
CCK	Male	35	667,34 ± 221,54	0,141
	Female	39	602,09 ± 132,00	
ANP	Male	35	2836,58 ± 2393,35	0,063
	Female	39	3636,44 ± 2272,01	
ACTH	Male	35	2681,09 ± 4607,89	0,176
	Female	39	3539,66 ± 4873,93	

*P<0,05 significant. *CCK: Cholecystokinin; ANP: Atrial natriüretik peptid; ACTH: Adrenocorticotropic Hormone*

DISCUSSION

An important aspect of stress physiology is regulated by hormones, such as ACTH, glucocorticoids, catecholamines, prolactin play a role in the stress response. Adrenal glands play a key role in hormonal responses to stress. The adrenal glands function on both the sympathetic nervous system and the HPA axis [9,17].

In a study showing that stress factors trigger the adrenal gland, leading to an increase in the release of glucocorticoids and/or catecholamines. It was stated that the increase in these hormones constitutes a front line of defense to protect the organism against stress conditions [17]. In a different study conducted on nurses working shifts, it was found that cortisol levels and anxiety frequency were significantly higher in those working at night compared to those working during the day. The research was conducted on nurses in the same age group, and it was stated that the higher cortisol and anxiety levels in night workers were not attributed to age differences [18]. In our study, we did not find a significant difference in the ACTH levels before the internship and at the end of the internship (p = 0.087). This result was not consistent with the literature. We believe this situation arises from the heightened activity of ANP, which suppresses the HPA pathway to reduce the anxiety experienced by intern doctors in the emergency department. The level of ACTH is significantly higher in female intern doctors after the internship compared to before. These differences could be due to the relationship between sex hormones, such as estrogen, and ACTH through the HPA pathway. We think that further research is needed to better explain this situation.

It is accepted that ANP functions as a neuropeptide in the nervous system [10,12]. It is stated that it suppresses the HPA system at almost every stage under stress conditions [10,14]. In two different studies conducted on patients with panic attacks, it was shown that ANP limits panic attacks and that high ANP levels during the attack are associated with low anxiety levels. It has been stated that ANP limits panic attacks by suppressing the HPA pathway and reducing the CCK4 level [19,20]. Studies on patients with predominantly heart-related issues have indicated that anxiety and depression symptoms decrease as the ANP level rises as a result of physical activity (exercise) [21,22]. It has been shown that the level of ANP is inversely proportional to depression and anxiety scores in patients with heart failure. Additionally, depression and anxiety scores decrease as the ANP level increases [23]. In another study on patients with congestive heart failure, the researchers used the HADS (Hospital Anxiety and Depression Scale) to measure anxiety levels. The study demonstrated that the HADS score decreased as the levels of ANP and Pro ANP increased [24]. In our study, we found that the levels of ANP in intern doctors were significantly higher after their internship than before ($p=0.001$). No statistically significant difference was detected between gender groups and the result was consistent with the literature. The response of ANP to stress factors can be better understood through additional studies. We believe these studies can help in identifying and treating stress. CCK is thought to play a role in panic attacks, a type of anxiety disorder. It has been demonstrated that CCK-B receptor agonists, like CCK4, trigger panic attacks, while CCK-B receptor antagonists produce anxiolytic effects [10,11,28]. Peptides such as CRF, leptin, orexin, neuropeptide y and CCK have been found to impact both nutrition and the stress response [25,26]. CCK receptors are mainly found in the mesolimbic structures, hypothalamus, and brainstem nuclei in the brain. Dopamine, glutamate, serotonin, and neuropeptides interact with these receptors. It has been demonstrated that CCK receptors in the raphe nucleus control the impact of serotonin, and it has been proposed that CCK receptors could be utilized in the additional treatment of schizophrenia and mood disorders [27]. It has been shown that CCK4 induces panic attacks by acting on GABA-A receptors in patients with panic attacks [28]. In our study, we found that CCK levels in intern doctors at the end of the internship were significantly higher than before the internship. We did not detect any difference between genders. This result, which is supported by the literature, may have a positive effect on determining the anxiety state.

The study results might have been different if it had been carried out at different centers with different intern doctors, since the results could vary based on the participants' personality traits.

CONCLUSION

While the hormone levels measured after the internship show a rather anxiolytic picture (no change in ACTH level, increased ANP). The higher BAI score after the internship can be explained by the fact that BAI is a subjective evaluation. The role of CCK in anxiety is still controversial. While CCK B receptor agonists such as CCK 4 have an anxiety-increasing effect, CCK B receptor antagonists have an anxiolytic effect. In our study, CCK levels after the internship were found to be significantly higher than before the internship.

Identifying the hormones that increase or decrease during stressful circumstances, as well as conducting further research on treatment for this subject, may be one of the most important stages in developing coping methods for stress. It is clear that more detailed research is needed for all three hormones.

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Availability of Data and Materials: Submitted work is original and has not been published elsewhere in any language.

Informed Consent: Written consent was obtained from all intern doctors included in the study.

Competing Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical Approval: Before the study, we obtained approval from the Gaziantep University Faculty of Medicine Ethics Committee (Ethics committee decision no: 2017/162, date: 26.04.2017).

Human Rights

The study protocol was conducted in accordance with the Declaration of Helsinki.

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Original Research

Correlation of Imaging and Histopathological Findings

Elif Sari [1], Aynur Aliyeva [2,3*]

[1] Department of Otorhinolaryngology-Head and Neck Surgery Istanbul Aydın University VM Medikal Park Florya Hospital, Istanbul, Türkiye
[2] Division of Otorhinolaryngology-Head and Neck Surgery, The Catholic University St.Mary Hospital Medical Center, Seoul, South Korea
[3] The Neuroscience Doctoral Program, Yeditepe University, Istanbul, Türkiye

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Corresponding Author
Aynur Aliyeva, MD, PhD
Address: Department of Otorhinolaryngology-Head and Neck Surgery
The Catholic University St.Mary Hospital Medical Center, Seoul, South Korea
E-mail: dr.aynuraliyeva86@gmail.com

ABSTRACT

Objective: Head and neck cancers are diagnostically complex, with lymph node metastasis significantly impacting prognosis and clinical management. The presence of lymph node involvement drastically reduces survival rates, making its accurate detection critical. Standard diagnostic tools such as CT, MRI, and PET-CT are widely used to assess tumor extent, lymph node involvement, and cartilage invasion. However, limited studies exist correlating physical examination, imaging findings, and histopathological results. This study aims to evaluate these correlations in head and neck cancer patients who underwent surgery.

Methods: A retrospective analysis was performed on 48 patients with head and neck cancers. Data collection included demographic details, cancer type, physical examination findings, imaging results (CT, MRI, PET-CT), and histopathological evaluations. Statistical analyses included sensitivity, specificity, and correlation coefficients for each diagnostic method, with pathology as the gold standard. Descriptive statistics, chi-square tests, and correlation analyses were used to determine diagnostic accuracy.

Results: The median age of the patients was 60.15 years (±9.57), with 41 males (85.42%) and seven females (14.58%). The most common cancer type was larynx cancer (62.5%), followed by tongue cancer (14.6%). Physical examination identified right neck positivity in 25% and left neck positivity in 16.67% of cases. CT/MRI showed right neck positivity in 31.25% and left neck positivity in 25%, while PET-CT showed 8.33% right neck and 6.25% left neck positivity. CT/MRI had the highest sensitivity (70%) and specificity (75%) for neck positivity, while PET-CT was less sensitive but complementary for cases missed by physical exams.

Conclusion: This study highlights the complementary roles of physical examinations, CT, MRI, and PET-CT in diagnosing head and neck cancers. CT/MRI demonstrated superior sensitivity and specificity in detecting cartilage invasion and lymph node involvement, particularly for larger tumors. PET-CT proved useful in detecting smaller or metabolically active tumors. Accurate diagnosis requires an integrated approach combining multiple diagnostic modalities.

Keywords: Head And Neck Cancer, Diagnostic Imaging, CT/MRI Accuracy, PET-CT Sensitivity, Lymph Node Metastasis Detection

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INTRODUCTION

Head and neck cancers are challenging malignancies that require precise diagnostic and therapeutic approaches [1-3]. Surgical approaches for these patients are based on physical examination and radiological imaging findings [4]. Lymph node metastasis is a critical factor in prognosis and clinical decisions, significantly affecting survival rates [5]. Five-year survival is around 65% without lymph node metastasis but drops to 29% with it, making its detection crucial. Contrast-enhanced CT and MRI are standard for staging, with lymph nodes over 1 cm often considered metastatic, though up to 40% may be smaller. MRI shows 75% sensitivity and 63% specificity for detecting metastatic nodes, while CT has 35% sensitivity and 100% specificity. FDG-PET detects glucose metabolism in tumor-infiltrated nodes regardless of size, with 87%-94% sensitivity and 94%-100% specificity for regional metastasis [6-10]. Compared to CT and MRI, FDG-PET/CT can alter lymph node staging in about 20% of cases [10-12].

Patients with anterior commissure involvement in laryngeal cancer require thorough evaluation, as it impacts both staging and surgical planning. Radiological assessments help detect cartilage erosion and invasion, with MRI showing higher sensitivity than CT for neoplastic cartilage invasion, though less specific. MRI may overestimate invasion, leading to overtreatment, while CT can underestimate it, risking inadequate treatment. Accurate evaluation of anterior commissure invasion during surgery is crucial to avoid improper intervention [13,14].

Main Points

The study evaluates how well physical exams, CT/MRI, and PET-CT detect lymph node metastasis and cartilage invasion in head and neck cancers. CT/MRI was the most accurate, especially for larger tumors, while PET-CT added value for smaller, metabolically active lesions.

CT/MRI correlated strongly with pathology results, confirming its importance in assessing disease extent and guiding surgery.

Physical exams alone had limited sensitivity for smaller tumors, highlighting the need for advanced imaging to improve diagnostic accuracy.

PET-CT, though less sensitive for cartilage invasion, was useful in detecting smaller tumors missed by CT/MRI, proving valuable in complex cases.

Combining physical exams with CT, MRI, and PET-CT improves diagnosis and treatment planning, especially for lymph node and cartilage involvement, leading to better outcomes.

While previous studies have compared CT, MRI, and PET-CT for evaluating cartilage invasion and lymph node involvement, few correlate physical exam findings with histopathological outcomes [13-15]. This study seeks to fill the gap in the literature by evaluating the correlation between physical examination, radiological imaging, and histopathological findings in patients with head and neck cancers who have undergone surgery. Its primary objective is to analyze the relationship among these diagnostic approaches, while the secondary goal is to compare the findings to existing studies, thereby addressing a critical deficiency in understanding diagnostic strategies for head and neck cancers.

MATERIALS AND METHODS

Study Design

This retrospective chart review of this study compares physical examination findings, radiological imaging (CT, MRI, PET-CT), and histopathological results in patients with head and neck cancers. The Ethics Committee of xxx the study. Data were collected from patient records at the xxx ENT clinic between September 1, 2021, and September 1, 2023. The study aims to evaluate the correlation between clinical, radiological, and histopathological findings to improve diagnostic accuracy and treatment planning.

Study Population

The study included patients diagnosed with head and neck cancer who underwent surgery at the clinic during the study period. The inclusion criteria for the study were:(1) patients diagnosed with head and neck cancer, (2) patients aged 18 years or older, and (3) patients who underwent surgical intervention. The exclusion criteria were:(1) patients under the age of 18,(2) pregnant or breastfeeding women, and (3) patients with a concurrent second malignancy. Patients meeting any exclusion criteria were excluded during the data collection process.

Study Procedures

For each patient, the following data were extracted from medical records: gender, the primary site of malignancy, the estimated size of the tumor during physical examination, and the presence and size of palpable lymph nodes during neck examination. CT, MRI, and PET-CT imaging reports, as well as

histopathological findings post-surgery, were retrieved. Physical examination findings were correlated with radiological imaging (size of primary tumor, lymph node reactivity, thyroid or cricoid cartilage invasion) and final histopathological outcomes.CT, MRI, and PET-CT scans were utilized to evaluate the extent of the tumor and its spread to surrounding tissues and lymph nodes. Those reports were also included in cases where whole-body PET-CT was conducted. Radiological features such as the size and reactivity of lymph nodes, the extent of primary tumors, and any evidence of cartilage invasion were documented and compared to histopathological results.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25—descriptive statistics summarized age, gender, and cancer type. Chi-square and Fisher's Exact tests evaluated gender distribution and compared positivity rates across diagnostic methods (physical exam, CT/MRI, PET-CT, and pathology), with p-values determining statistical significance. Proportions were calculated for neck positivity and cartilage invasion. Pearson and Spearman correlation analyses assessed relationships between pathology and imaging results. Sensitivity and specificity were calculated using pathology as the gold standard, and mass size correlations were analyzed using Pearson/Spearman tests. Chi-square tests evaluated detection accuracy for different cancer types and gender differences.

RESULTS

1. Demographic Data

The median age of 48 patients was 60.15, with a standard deviation of ±9.57. The youngest patient was 27, and the oldest was 76. Regarding gender distribution, there were 41 males (85.42%) and seven females (14.58%).

The most common cancer type observed was larynx cancer, with 30 cases (62.5%), followed by tongue cancer with 7 cases (14.6%). Tonsil and oropharynx cancers were each present in 2 cases (4.2%). Gingiva, lip, palatine, maxilla, and thyroid cancers were each represented by 1 case (2.1%).

2. Physical Examination, Imaging (CT/MRI and PET CT), Pathology Positivity. (Table 1)

In the physical examination, right neck positivity was observed in 12 out of 48 cases (25%), left neck positivity in 8 cases (16.67%), and total neck positivity (right + left) was 20 cases (41.67%).

Table 1. Comprehensive Results

Parameter	Physical Exam	CT/MRI	PET-CT	Pathology	p-value
Right Neck Positivity (%)	25% (12/48)	31.25% (15/48)	8.33% (4/48)	37.5% (18/48)	<0.05
Left Neck Positivity (%)	16.67% (8/48)	25% (12/48)	6.25% (3/48)	18.75% (9/48)	<0.05
Total Neck Positivity (%)	41.67% (20/48)	56.25% (27/48)	14.58% (7/48)	56.25% (27/48)	<0.05
Cartilage Invasion (%)	29.17% (14/48)	29.17% (14/48)	10.42% (5/48)	27.08% (13/48)	<0.05
Sensitivity (%)	45%	70%	50%	N/A	N/A
Specificity (%)	60%	75%	65%	N/A	N/A
Mass Size (Length, mm)	23.96 ± 7.93	30.38 ± 11.10	25.87 ± 11.61	28.15 ± 10.63	<0.05
Mass Size (Length, mm)	23.96 ± 7.93	30.38 ± 11.10	25.87 ± 11.61	28.15 ± 10.63	<0.05
Mass Size (Length, mm)	23.96 ± 7.93	30.38 ± 11.10	25.87 ± 11.61	28.15 ± 10.63	<0.05
Larynx Cancer Detection (%)	68%	82% ($p < 0.05$)	68%	100% (Gold Standard)	<0.05
Tongue Cancer Detection (%)	60%	75%	60%	100% (Gold Standard)	>0.05
Tongue Cancer Detection (%)	60%	75%	60%	100% (Gold Standard)	>0.05

For CT/MRI, right neck positivity was found in 15 out of 48 cases (31.25%), left neck positivity in 12 cases (25%), and total neck positivity in 27 cases (56.25%). Cartilage invasion was noted in 14 cases (29.17%).

In PET CT, right neck positivity was present in 4 out of 48 cases (8.33%), left neck positivity in 3 cases (6.25%), and total neck positivity in 7 cases (14.58%). Cartilage invasion was positive in 5 cases (10.42%).

Pathology results indicated right neck positivity in 18 out of 48 cases (37.5%), left neck positivity in 9 cases (18.75%), and total neck positivity in 27 cases (56.25%). Cartilage invasion was observed in 13 cases (27.08%).

3. Correlation of Pathology Positivity with Physical Exam, CT/MRI, and PET CT Positivity

Among patients with positive pathology for the right neck, 38.89% (7/18) were positive on both physical exam and CT/MRI, and 22.22% (4/18) on all three modalities (physical exam, CT/MRI, PET-CT). For the left neck, 33.33% (3/9) were positive on both physical exam and CT/MRI, and 22.22% (2/9) on all three. In total neck involvement, 37.04% (10/27) were positive on both physical exam and CT/MRI, with 22.22% (6/27) on all three. For cartilage invasion, 61.54% (8/13) were positive on both physical exam and CT/MRI and 30.77% (4/13) on all three.

4. Correlation Between Physical Exam, CT/MRI, PET CT, and Pathology Reports

The correlation between physical exam positivity and pathology findings was moderate ($r \approx 0.3$), while CT/MRI demonstrated a higher correlation with pathology results ($r \approx 0.6$). PET-CT showed a slightly lower correlation with pathology results ($r \approx 0.5$). The p-values for the correlation between pathology and CT/MRI were statistically significant ($p < 0.05$), indicating strong diagnostic accuracy, while PET-CT showed borderline significance in some cases.

5. Specificity and Sensitivity Based on Pathology as Gold Standard

This study calculated the sensitivity and specificity of physical examination, CT/MRI, and PET CT using pathology results as the gold standard. Sensitivity was defined as the proportion of true positives detected by each modality, while specificity was the proportion of true negatives correctly identified.

The sensitivity was calculated for physical examination at ~45% and specificity at ~60%. CT/MRI showed higher diagnostic accuracy with a sensitivity of ~70% and specificity of ~75%. Though less sensitive than CT/MRI, PET CT demonstrated a sensitivity of ~50% and specificity of ~65%.

These findings indicate that CT/MRI had the highest diagnostic accuracy in detecting neck and cartilage pathology, while PET CT, though moderately sensitive, was particularly useful for detecting cases missed by physical examination. The results highlight the utility of imaging techniques, especially CT/MRI, in complementing physical examination for accurate diagnosis of head and neck cancers

6. Correlation Between Mass Sizes in Physical Exam, CT/MRI, PET CT, and Pathology

Mass size correlation showed that larger masses (mean >30 mm) were more accurately detected by physical examination, with a sensitivity of approximately 60%. In contrast, imaging methods such as CT/MRI and PET-CT were more effective in identifying smaller masses (<20 mm), with CT/MRI achieving around 70% sensitivity. Specifically, the average mass size for physical examination was 23.96 mm in length, while for CT/MRI, it was 30.38 mm, and for PET-CT, it was 25.87 mm. Pathology showed an average mass size of 28.15 mm. These results highlight that imaging is more sensitive for smaller tumors, complementing the effectiveness of physical exams for larger masses.

7. Correlation Between Pathological Diagnoses and Detection Accuracy by Imaging Method

Larynx Cancer: Best detected by CT/MRI with an accuracy of 82% ($p < 0.05$), followed by PET CT with an accuracy of 68%**.** The statistical significance (p-value) reflects the higher accuracy of CT/MRI in detecting larynx cancer compared to PET CT and physical examinations.

Tongue Cancer: CT/MRI showed the highest accuracy at 75%**,** followed by PET CT at 60%**.** While CT/MRI was more reliable for tongue cancer detection, the difference between methods did not reach statistical significance ($p > 0.05$).

Other Cancers (e.g., Gingiva, Lip): These cancers were better detected through physical examinations and pathology correlation, achieving an accuracy of around 68%**,** as smaller mass sizes and surface involvement make them easier to palpate and correlate with pathology results.

8. Cartilage Invasion Detection Sensitivity and Specificity

For detecting cartilage invasion, CT/MRI demonstrated a sensitivity of 85% and a specificity of 72%, while PET CT showed a sensitivity of 62% and a specificity of 66%**.** Sensitivity was calculated by dividing true positives by the sum of true positives and false negatives, representing the test's ability to correctly identify cases with cartilage invasion. Specificity was calculated by dividing true negatives by the sum of true negatives and false positives, reflecting the accuracy in identifying patients without cartilage invasion. CT/MRI outperformed PET CT in sensitivity and specificity, indicating its higher diagnostic accuracy for cartilage invasion detection.

DISCUSSION

Imaging and pathology are essential in managing head and neck cancers, particularly for diagnosis and treatment planning. Accurate staging is critical for prognosis, especially for lymph node involvement and cartilage invasion. In our study, CT and MRI were highly influential in detecting lymph node metastasis and cartilage invasion, especially for larger tumors. Consistent with Leslie et al. [6], MRI showed greater sensitivity for soft tissue involvement (82% accuracy for larynx cancer, $p < 0.05$), while CT excelled in specificity, particularly for recurrent disease. Our results align with Leslie et al.'s, showing MRI's superior sensitivity (75%) and CT's greater specificity (63%) for metastatic nodes. Though less sensitive, PET-CT complemented CT and MRI, especially for smaller or metabolically active tumors. CT/MRI had sensitivity and specificity of 85% and 72% for cartilage invasion, respectively. While less sensitive (62%), PET-CT offered valuable metabolic data. These findings highlight the importance of combining structural and functional imaging for optimal diagnosis and treatment.

It's essential to highlight the role of PET-CT in detecting head and neck cancers, particularly in the context of lymph node metastasis and recurrence, as explored in the literature [15]. Vermeersch et al. [7] demonstrated that FDG PET-CT offers added value over conventional imaging techniques, being more sensitive and specific in detecting cervical lymph node involvement (CLNI) and recurrent squamous cell carcinoma of the head and neck (SCCHN). In our study, PET-CT showed its strength in detecting metabolically active tumors and provided complementary insights when CT and MRI missed smaller lesions. These findings underscore the importance of PET-CT as a valuable tool in conjunction with anatomical imaging for more comprehensive diagnosis and staging of head and neck cancers. While PET-CT was slightly less sensitive in our cartilage invasion detection (62% sensitivity), it still provided critical data for tumors that CT/MRI might overlook, supporting its inclusion in a multimodal diagnostic approach.

Dammann et al. [8] compared the effectiveness of 18 FDG PET, CT, and MRI in staging head and neck SCC, concluding that while MRI had the highest sensitivity for detecting primary tumors, PET added valuable metabolic data in equivocal cases, particularly for lymph node involvement. This aligns with our findings, where CT/MRI showed superior sensitivity for larger tumors and cartilage invasion, with PET-CT complementing the detection of smaller or metabolically active lesions. Like Dammann et al., our study emphasizes PET-CT's role in improving diagnostic confidence, especially in cases missed by CT or MRI. Both studies support a multimodal approach, integrating structural and functional imaging to optimize cancer treatment planning.

Ha et al. [11] emphasized the role of PET-CT fusion in staging and managing head and neck SCC, showing that PET-CT altered treatment plans in 31% of cases by upstaging tumors and identifying occult metastases. PET-CT proved especially valuable in both early- and advanced-stage diseases. Similar to our study, Ha et al. found PET-CT crucial in detecting nodal involvement and distant metastases, complementing CT/MRI. In our study, PET-CT demonstrated moderate sensitivity (62%) and specificity (66%) for cartilage invasion but was particularly effective for smaller, metabolically active tumors missed by other modalities. Both studies highlight the importance of a multimodal approach, with PET-CT providing critical metabolic insights in complex cases.

Zbären et al. [14] evaluated the accuracy of staging laryngeal cancer using clinical/endoscopic exams, CT, and MRI compared to histopathology. They found that clinical evaluation alone had low staging accuracy (55%), particularly in detecting invasion of critical areas like the anterior commissure and cartilage. Combined with CT or MRI, accuracy improved to 80% and 87%, respectively. MRI was more sensitive to cartilage invasion, though with more false positives, while CT was more specific but tended to underestimate invasion. Like their study, ours demonstrated that MRI had higher sensitivity for soft tissue and cartilage detection, while CT offered greater specificity. Both studies agree that combining diagnostic tools improves staging accuracy and informs better treatment decisions for head and

neck cancers.

Our study demonstrated that integrating physical examination, CT/MRI, and PET-CT significantly improves diagnostic accuracy for head and neck cancers, with CT/MRI achieving a sensitivity of ~70% for lymph node positivity and superior detection of larger tumors (>30 mm), complementing Veena Vishwanath et al.'s [16] findings that MRI excels in soft tissue characterization. At the same time, PET-CT enhances the detection of metabolically active smaller lesions, underscoring a multimodal approach for varying tumor sizes and types .

Becker's [17] study highlights the essential role of CT and MRI in detecting neoplastic cartilage invasion in laryngeal cancer, noting MRI's higher negative predictive value but acknowledging CT's practical use. Both modalities may yield false positives due to reactive inflammation. Our study also found that MRI had higher sensitivity, while CT was more specific, emphasizing the need for a combined imaging approach to improve diagnostic accuracy and treatment planning.

Limitations

The main limitation of our study is its retrospective design, which may introduce selection bias. The retrospective nature of this study introduces potential biases, mainly due to variations in imaging quality and interpretation across different institutions. The small sample size of 48 patients also limits generalizability. Additionally, variations in imaging quality and lack of consideration for different tumor subtypes may influence the results. Inconsistencies in histopathological evaluations could further affect the correlation between imaging and pathology.

Despite these challenges, the study underscores the practical value of integrating physical examinations with CT, MRI, and PET-CT in diagnostic workflows, enhancing the detection of diverse tumor sizes and types while providing critical insights to inform more precise and effective treatment planning for head and neck cancers, ultimately improving patient care.

CONCLUSION

This study underscores the importance of combining physical exams with imaging techniques like CT, MRI, and PET-CT to accurately diagnose head and neck cancers. While physical exams are practical for larger tumors, CT/MRI and PET-CT improve precision, particularly for smaller lesions and cartilage invasion. CT/MRI showed the highest sensitivity and specificity, with PET-CT adding value in detecting metabolic activity. The strong correlation between imaging and pathology supports their key role in guiding treatment. Further research is needed to confirm these findings and refine diagnostic strategies.

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

Informed Consent: All the participants provided written informed consent to participate in the study.

Data availability statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval: Ethical approval for this study was obtained from Istanbul Aydın University (Approval No: 2023/152 at 29.11.2023). The study followed the guidelines outlined in the Declaration of Helsinki, and informed consent was obtained from all patients before their inclusion in the study.

Author Contributions:

Conception: ES, AA; Design: ES, AA; Supervision: ES, AA; Fundings: None; Materials: ES, AA; Data Collection and Processing: ES, AA; Analysis and Interpretation: AA; Literature: ES, AA; Review: ES, AA; Writing: AA, ES; Critical Review: ES, AA.

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Original Research

Recurrence and Factors Associated with Recurrence in Dupuytren's Disease Patients Treated with Percutaneous Needle Aponeurotomy

Muhammed Köroğlu[1], Kadir Ertem[1], Ekrem Özdemir[2], Gültekin Taşkıran[3], Mustafa Karakaplan[1], Emre Ergen[1], İpek Balıkçı Çiçek[4], Hüseyin Utku Özdeş[1,*], Okan Aslantürk[1]

[1] Department of Orthopaedics and Traumatology, Inonu University Faculty of Medicine, Malatya, Türkiye
[2] Department of Orthopaedics and Traumatology, Erzurum City Hospital, Erzurum, Türkiye
[3] Department of Orthopaedics and Traumatology, Antalya City Hospital, Antalya, Türkiye
[4] Department of Biostatistics, Inonu University Faculty of Medicine, Malatya, Türkiye

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Corresponding Author
Hüseyin Utku Özdeş, MD
Address: University Faculty of Medicine, Department of Orthopaedics and Traumatology, Malatya, Türkiye
E-mail: dr.utkuozdes@gmail.com

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ABSTRACT

Abstract

Objective: Dupuytren›s disease (DD) is a progressive condition of the palmar fascia that limits finger extension. Percutaneous needle aponeurotomy has become increasingly popular in recent years. Despite appropriate treatment, recurrence is common. This study investigates recurrence development following percutaneous needle aponeurotomy and evaluates the relationship between patient characteristics, disease-related factors, and recurrence in DD.

Methods: This retrospective study included 98 fingers from 41 patients diagnosed with Dupuytren›s disease who underwent percutaneous needle aponeurotomy at a hand surgery outpatient clinic between 2012 and 2022. Patient records were reviewed, and characteristics such as age, gender, occupation, and dominant hand were documented. The stage of DD was determined preoperatively. Functional outcomes were assessed using a subjective satisfaction scale, and postoperative complications and recurrences were analyzed.

Results: Of the 41 patients, 32 (78%) were male and 9 (22%) were female. The mean age was 62 years (range, 44–82 years), and the mean follow-up period was 45 months (range, 9–138 months). Postoperative evaluations showed that 17 patients (41.5%) had excellent results, 19 patients (46.3%) had good results, and 5 patients (12.2%) had fair results. Recurrence of Dupuytren›s disease occurred in 24 (58.5%) patients. Among all patients, 30 (73.2%) were willing to undergo reoperation, regardless of recurrence. The recurrence rate was significantly lower after percutaneous needle release in stage 1 DD ($p = 0.011$).

Conclusion: Percutaneous needle aponeurotomy offers high patient satisfaction and early discharge benefits, making it a preferred option for surgeons, despite the potential for recurrence. While the classification of recurrence as a complication is debated, it is a recognized outcome of progressive DD. Regardless of patient characteristics, performing percutaneous needle aponeurotomy at an early stage can significantly reduce recurrence rates.

Keywords: Dupuytren, percutaneous needle aponeurotomy, recurrence

INTRODUCTION

Dupuytren's disease (DD) is a chronic condition marked by progressive fibrosis of the palmar aponeurosis, resulting in flexion contracture of the fingers [1]. Genetic predisposition plays a role in the development of this insidious disease, but the exact underlying causation remains unclear [2,3]. Several treatment options are currently available for DD, which is still regarded as idiopathic, including needle aponeurotomy, collagenase injection, and open fasciectomy [4]. Minimally invasive techniques such as percutaneous needle aponeurotomy and collagenase injection have gained popularity and are often preferred by hand surgeons over open surgery due to the advantages of fewer complications, simpler technique and faster postoperative recovery [5,6]. Despite the success of percutaneous needle aponeurotomy, the major challenge remains the recurrence of the disease. Due to the progressive nature of DD, recurrence is common, regardless of the treatment method.

This study investigates potential factors influencing recurrence in patients who have undergone percutaneous needle aponeurotomy. By examining demographic characteristics and disease-related factors in patients with recurrence, we aim to identify any factors that may contribute to the recurrence of DD.

MATERIALS AND METHODS

Ethical approval was obtained from the ethics committee of 2024/6242 University for this study. The study was conducted in a single centre and was retrospective.

Main Points

- Dupuytren's disease is a progressive, chronic disease that causes dysfunction rather than pain in the hand.
- Percutaneous needle aponeurotomy is a more comfortable procedure than open surgery with rapid results.
- Although percutaneous needle aponeurotomy provides satisfactory functional results, recurrent disease may occur.
- Patients should be informed about the recurrence in percutaneous needle loosening in late stage Dupuytren's disease.

Patient Selection

Patients who were admitted to the hand surgery outpatient clinic between 2012 and 2022 with a diagnosis of Dupuytren's disease and underwent percutaneous aponeurotomy surgery, with a minimum follow-up period of 9 months and older than 18 years of age, and patients with complete file records (hospital electronic file) and regular follow-up (Dupuytren follow-up file) were included in the study. Patients who were diagnosed with Dupuytren's disease but underwent open fasciectomy, had incomplete hospital records or irregular follow-up and could not be reached, and patients with a history of previous hand surgery or other hand pathology in addition to Dupuytren's disease were excluded from the study.

Of the 113 patients with Dupuytren's disease identified in our clinic records, 41 met the inclusion criteria, and 98 fingers of these patients were evaluated.Patients were routinely evaluated in the hand surgery clinic and diagnosed with DD through clinical examination. If there were no additional complaints, no further tests or imaging methods were performed. Demographic data, including age, gender, occupation involving repetitive hand use, and dominant hand, were recorded. A detailed medical history was also taken, covering conditions associated with DD, such as diabetes mellitus, and lifestyle factors like smoking, alcohol use, and chronic medication use. Conditions with similar pathogenesis to DD, such as Ledderhose disease, Garrod's pads, and Peyronie's disease, were documented. Hand examinations were conducted to assess the presence of cords and nodules related to DD, and the affected fingers were identified. The disease stage was classified preoperatively using the Tubiana classification [7] (Table 1). The percutaneous needle release technique was explained to all patients, and written and verbal consent for surgery was obtained.Patient satisfaction was assessed using a subjective satisfaction score based on the self-assessment of function, activities of daily living, and quality of life after orthopedic intervention, with outcomes categorized as excellent, good, fair, or poor. Patients who experienced recurrence were identified, and the relationships between recurrence and factors such as preoperative disease stage, age, gender, presence of additional involvement, occupation, smoking, medication use, and comorbidities were analyzed. Functional outcomes for patients who developed recurrence were examined, and their interest in repeat surgery was recorded. The average time to recurrence was calculated, and postoperative complications were documented.

Table 1. Tubiana classification [7]

Stage	Deformity
Stage 0	No extension deficit
N	N describes a nodul, but without contracture
Stage 1	contracture between 0-45 degrees
Stage 2	contracture between 45-90 degrees
Stage 3	contracture between 90-135 degrees
Stage 4	contracture greater than 135 degrees

Surgical Technique

The surgery was performed under local anesthesia without the use of a tourniquet. The hand to be treated was washed with an antiseptic solution and then painted with Betadine before being covered with sterile drapes. The Dupuytren cords and nodules were marked with a pen (Figure 1-2). Local anesthesia was applied over the cord and at the needle entry site subcutaneously. The anesthesia was applied very superficially to prevent nerve damage, a possible complication during the intraoperative percutaneous needle release. Throughout the procedure, feedback from the patient was sought to monitor for potential nerve damage. To prevent another complication of percutaneous aponeurotomy, skin tears, a minimum distance of 5 mm was maintained between release sites. The releases were performed at 2 or 3 levels and applied from distal to proximal. To avoid flexor tendon injury, the needle was placed in the release area, and the patient was asked to perform finger flexion and extension movements to determine the release level and protect the flexor tendon. We used three basic methods movements: clean, perforate and sweep. Needle once the needle was directed towards the dermis. Tangentially and in a plane between the dermis and the cord improved transversely at the level (cleared) the portal is at least as wide as the palpable cord width. Needle vertically reorientated, inclination transverse and slightly reciprocating (perforate) used to define movement, scope and surface cord geometry. Once the cord geometry defined, the needle tip inclination was used repeatedly sweep or scrape the surface of the cord. In the meantime fingers were held in extension position, We changed the needles at frequent intervals to maintain its sharpness needle. After releases were made in several areas, the fingers were hyperextended to free any remaining cord attachments [6] (Figure 3-4). We inject 1cc betamethasone in the released area to prevent the recurrence of the cord. The needle entry sites were covered with gauze, and the hands were wrapped with bandages, to be removed the next day. Patients were discharged on the same day. They were informed about possible early complications such as infection, hematoma, and prolonged edema, and provided with relevant advice.We recommend patients to use an extension splint at night for 2 months. We retrospectively used follow-up data from outpatient clinic visits at 2 weeks, 6 weeks, 3 months, 6 months, and 12 months postoperatively.

Figure 1. The 4th and 5th fingers of the right hand affected by Dupuytren's disease. Preoperative marking of cords and nodules.

Figure 2. Lateral profile view of the hand. Early stage flexion contracture

Figure 3. Anterior view of the hand after percutaneous needle release

Figure 4. Gain of extension in the fingers after release procedure

Statistical Analysis

Qualitative variables were summarized as numbers (percentages). The normality of the distribution of quantitative variables was assessed using the Shapiro-Wilk test. Quantitative data that did not show a normal distribution were summarized as median (minimum-maximum), while those that showed a normal distribution were summarized as mean ± standard deviation. For statistical analysis, categorical variables were compared using Pearson's chi-square test, Yates' corrected chi-square test, and Fisher's exact chi-square test. For quantitative variables, the Mann-Whitney U test was used for comparisons between two independent groups when appropriate. A p-value of <0.05 was considered statistically significant in the analyses. All analyses were performed using IBM SPSS Statistics 26.0 for Windows (New York, USA). Within the scope of the study, it is aimed to evaluate the relationship between the development of recurrence after percutaneous needle aponeurotomy and the characteristics of patients, disease-related factors, and recurrence in Dupuytren's disease. According to the theoretical power analysis conducted using the G*Power 3.1 program, in comparing the recurrence of postoperative outcomes with the preoperative clinical stage, one of the significant output variables, the Type I error rate (alpha) is 0.05, the power of the test (1-beta) is 0.8, the effect size is 0.5, and the degrees of freedom (df) is 2. Therefore, the minimum sample size required to find a significant difference using the multigroup: Goodness of fit test should be a total of 39 patients.

RESULTS

Of the 41 patients, 32 (78%) were male, and 9 (22%) were female. The mean age was 62 years, ranging from 44 to 82 years. The mean follow-up period was 45 months, with a range from 9 to 138 months. The dominant hand was the right in 38 patients (92.7%) and left in 3 patients (7.3%). The demographic data, including gender, habits, comorbidities, and findings related to DD, are detailed in Table 2. During follow-up, 24 out of 41 patients (58.5%) experienced a recurrence of DD and a total of 98 fingers were operated. And recurrence was found in 38 fingers. Preoperative stage 3 disease was found in 15 fingers with recurrence, while 18 fingers had stage 2 and 5 fingers had stage 1 DD. The mean time to recurrence was 30.4 months, ranging from 2 to 84 months. Clinical outcomes showed that 30 of the 41 patients (73.2%) were willing to undergo reoperation, irrespective of recurrence status. The relationship between recurrence and patient characteristics is detailed in Table 3. Postoperative recurrence was higher in males (82.6%) compared to females (17.4%), but this difference was not statistically significant ($p = 0.702$). Recurrence rates were similar among laborers, office workers, and housewives ($p = 0.911$). Although recurrence rates were higher in patients with the right hand as the dominant hand, this difference was not statistically significant ($p = 0.254$). There was also no significant difference in recurrence rates among patients with right, left, or bilateral finger involvement ($p = 0.684$).In terms of preoperative clinical stage, the rate of no recurrence in stage 1 patients was 58.8%, while the recurrence rate was 20.8%, and

this difference was statistically significant (p = 0.011). There was no statistically significant difference in recurrence rates for patients in stages 2 and 3.Although the recurrence rate was higher in patients with diabetes mellitus (DM), this difference was borderline statistically significant (p = 0.052). No significant difference was observed between patients with and without postoperative recurrence in terms of comorbidities and family history (p = 0.724 and p = 0.679, respectively). The presence of additional lesions did not affect postoperative recurrence (p = 1.000). Although the recurrence rate was higher in smokers, the difference was not statistically significant (p = 0.123). There was no significant difference in terms of medication use (p = 0.724).When the subjective satisfaction results of the patients were analyzed, 17 patients (41.5%) had excellent results, 19 patients (46.3%) had good results, and 5 patients (12.2%) had fair results. No patient reported poor results after surgery. No early complications were observed in any patient. In 2 patients (4.9%), loss of sensation in the operated area and web space was observed as a late complication; however, the clinical results of these patients were rated as 'good' by subjective evaluation. No significant difference was observed in terms of reoperation demand with postoperative recurrence (p = 0.736). Patients with recurrence were willing to undergo reoperation.

Table 2. Demographic data of the patients and data for Dupuytren's disease

	n	%
Gender		
Male	32	78.0
Woman	9	22.0
Occupation		
Labourer	20	48.8
Office Worker	13	31.7
Working at home	8	19.5
Smoking		
Positive	14	34.1
Negative	27	65.9
Diabetes		
Positive	18	43.9
Negative	23	56.1
Family history		
Positive	7	17.1
Negative	34	82.9
Dominant Hand		
Right	38	92.7
Left	3	7.3
Dupuytren'sDisease side		
Right	14	34.1
Left	12	29.3
Bilateral	15	36.6
Clinical Stage		
Stage 1	15	36.6
Stage 2	19	46.3
Stage 3	7	17.1
Additional lesions (Gorrod' pad, Peyronie, Ledderhose)		
Positive	10	24.4
Negative	31	75.6

Table 3. Recurrence and its relation with patient characteristic

	Recurrence n(%)		p
	Positive	**Negative**	
Age			
Under 55 years	7 (29.2%)	2 (11.8%)	0.262
Over 55 years	17 (70.8%)	15 (88.2%)	
Gender			
Male	19 (79.2%)	13 (76.5)	0.702
Female	5 (20.8%)	4 (23.5)	
Dominant Hand			
Right	21 (87.5%)	17 (100.0%)	0.254
Left	3 (12.5%)	0 (0.0%)	
Occupation			
Labourer	12(50.0%)	8 (47.1%)	
Office Worker	7(29.2%)	6 (35.3%)	0.911
Working at home	5(20.8%)	3 (17.7%)	
Diabetes			
Positive	7 (29.2%)	11 (64.7%)	0.052
Negative	17 (70.8%)	6 (35.3%)	
Smoking			
Positive	11 (45.8%)	3 (17.6%)	0.123
Negative	13 (54.2%)	14 (82.4%)	
Clinical Stage			
Stage 1	5 (20.8%)	10 (58.8%)	
Stage 2	12 (50.0%)	7 (41.2%)	**0.01**
Stage 3	7 (29.2%)	0 (0.0%)	
Family history			
Positive	5 (20.8%)	2 (11.8%)	0.679
Negative	19 (79.2%)	15 (88.2%)	
Additional lesions			
Positive	6 (25.0%)	4 (23.5%)	1.0
Negative	18 (75.0%)	13 (76.5%)	
Hand affected			
Right	7 (29.17)	7 (41.18)	
Left	8 (33.33)	4 (23.53)	0.684
Bilateral	9 (37.50)	6 (35.29)	
Medications			
Has	13 (54.17)	11 (64.71)	0.724
None	11 (45.83)	6 (35.29)	
Comorbidity			
Has	13 (54.17)	11 (64.71)	0.724
None	11 (45.83)	6 (35.29)	

DISCUSSION

Postoperative complications of Dupuytren's surgery include infection, hematoma, digital nerve damage, and flexor tendon injuries. However, the recurrence of the deformity remains a topic of debate, as it is unclear whether it should be classified as a complication or a natural progression of the disease. The term "residual deformity" has been introduced for patients whose deformity persists after surgery or who experience recurrence within one year [8]. Even in the presence of a residual lesion, functional problems can persist. Recurrence is typically defined as an extension loss of more than 20 degrees or the presence of a palpable cord. The recurrence rate after percutaneous aponeurotomy has been reported in the literature to range from 9% to 65%, and it has been suggested that this rate could rise to as high as 85% in long-term follow-ups [9]. In a study, it was reported that recurrence after open surgery, injection and percutaneous release was most common in percutaneous release [10]. Although there are studies in the literature with relatively low rates of 12% after percutaneous aponeurotomy, open surgery has been found to be better in terms of recurrence in large-scale systematic reviews [11,12]. In our study, recurrence was observed in 24 patients (58.5%), and sensory loss was noted in 2 patients (4.88%). We found that the recurrence rate was lower after percutaneous aponeurotomy in Stage 1 DD ($p = 0.01$). When considering both modifiable and non-modifiable characteristics, the recurrence rate increases significantly after surgeries performed with percutaneous needle aponeurotomy after stage 1. In the literature, there are systematic reviews investigating recurrence rates and presenting results, but research on the causes is very limited [9].

A study comparing patients with Dupuytren's disease who underwent open fasciectomy and percutaneous needle aponeurotomy found similar levels of postoperative patient satisfaction [13]. Another study evaluating functional outcomes reported that the passive extension range was better in patients who underwent limited fasciotomy compared to those who had percutaneous release, although satisfaction scores for both procedures were similar. Notably, patients who had needle aponeurotomy achieved better Visual Analogue Scale (VAS) scores [14]. In a study where the reoperation rate for percutaneous surgery was reported as 29.7%, it was emphasized that patient satisfaction remained high and that patients had a positive attitude towards undergoing surgery again [15]. In our study, the satisfaction rate was approximately 90% based on subjective scoring, and 73.2% of patients expressed a willingness to undergo surgery again. In the literature, high satisfaction rates of up to 75% have been reported for the percutaneous aponeurotomy procedure [16]. Despite the relatively high rates of recurrence, percutaneous needle aponeurotomy is considered a successful method for many patients due to its advantages.

Dupuytren's disease is closely associated with factors such as alcohol use, smoking, antiepileptic medications, and diabetes, with family history being significant due to genetic factors [17]. A recent study confirmed that diabetes is a significant risk factor for Dupuytren's disease [18]. In our study, Dupuytren's disease was more common in patients with diabetes. Although the recurrence rate was higher in patients with diabetes compared to those without, this difference was not statistically significant. The lack of statistical significance may be related to the sample size; however, despite a higher recurrence rate in smokers, no positive correlation with recurrence was established. As we had no patients who used alcohol, this factor could not be evaluated.

Repetitive handwork, exposure to vibration, male gender, and a family history of the disease are also recognized risk factors for DD [19]. There is also an association between Dupuytren's disease and Peyronie's and Ledderhose diseases, which share similar pathogenesis [20]. However, studies exploring whether these factors also predict recurrence after surgery are limited. A study on recurrence after fasciectomy found that male gender, family history, onset of the disease before age 50, additional involvement, particularly Garrod's pads, and bilateral disease presence were significant for recurrence and associated with approximately threefold higher recurrence rates [21]. In patients who underwent partial fasciectomy, the onset of the disease at an older age was identified as a factor for recurrence [22]. In our study, no significant recurrence was detected in relation to family history of Dupuytren's disease or bilateral hand involvement. Consistent with the epidemiology of Dupuytren's disease, the number of primary cases was higher in males; however, no association was found between male gender and recurrence after percutaneous needle aponeurotomy. Among the 10 patients with Peyronie's disease, Ledderhose disease, or Garrod's nodules, which have similar pathogenesis to DD, there was no significant relationship in terms of recurrence. Additionally, no difference in recurrence rates was observed between workers and household employees in terms of repetitive hand use and vibration exposure.

This study has several limitations. It is primarily a single-center

study so, the patient and included finger numbers were limited and therefore power of the study was low . Secondly, it has a retrospective nature, and the follow-up period for detecting recurrence cases is relatively short thus it does not give us a cause and effect relation.. Finally, in Dupuytren's disease diagnosed through examination, there may be incomplete evaluations, and due to changes in the outpatient clinic doctors recording the data, there could be discrepancies in the extension measurements during preoperative staging.

In conclusion, DD is an insidious, progressive, and chronic condition. The percutaneous needle aponeurotomy procedure used in treatment offers high patient satisfaction. However, due to the nature of this disease, recurrence is quite common. The most significant factor affecting recurrence is the stage of Dupuytren's disease rather than patient characteristics such as age, gender, comorbidities, additional involvement, and bilateral involvement. Therefore, especially in advanced stage cases, patients should be informed about the risk of recurrence as part of patient management. Percutaneous needle aponeurotomy is quite safe in Stage 1 Dupuytren's surgery.

CONCLUSION

Percutaneous needle aponeurotomy is an effective treatment for Dupuytren's disease, offering high patient satisfaction and minimal invasiveness. However, recurrence remains a common outcome, particularly in advanced stages of the disease. This study highlights that performing the procedure at an early stage can significantly reduce recurrence rates, irrespective of patient demographics or comorbidities. These findings underscore the importance of early intervention and patient education about the potential for recurrence in managing Dupuytren's disease.

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Original Research

The Effect of Smoking on Gingival Crevicular Fluid Sclerostin and TNF-A Levels in Patient with Periodontitis

Mehmet Oguzhan Ergin[1,*], Kamile Erciyas[2], Mehmet Tarakçıoğlu[3], Hasan Ulusal[3]

[1] Department of Periodontology, Faculty of Dentistry, Harran University, Şanlıurfa, Türkiye
[2] Department of Periodontology, Faculty of Dentistry, Gaziantep University, Gaziantep, Türkiye
[3] Department of of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye

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Corresponding Author
Mehmet Oğuzhan Ergin, Assist. Prof.
Address: Department of Periodontology, Faculty of Dentistry, Harran University, Şanlıurfa, Türkiye
E-mail: oergin@harran.edu.tr; dtoguzhanergin@gmail.com

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ABSTRACT

Objective: The objective of this study was to evaluate the impact of cigarette smoking on sclerostin and TNF-α levels in subjects exhibiting periodontally healthy conditions and those afflicted with periodontitis. The hypothesis tested was that sclerostin levels in smokers could serve as a diagnostic marker and a tool to assess the progression of the disease.

Methods: In the present study, gingival crevicular fluid samples were obtained from a total of 72 patients, who were divided into four distinct groups: a control group of 18 non-smoking individuals without periodontitis, a group of 18 non-smoking individuals with periodontitis, a group of 18 healthy individuals who smoked, and a group of 18 smokers with periodontitis. The levels of sclerostin and TNF-α were then evaluated using the enzyme-linked immunosorbent assay (ELISA) method.

Results: The findings indicated a positive correlation between sclerostin and TNF-α levels in the gingival fluid of individuals diagnosed with periodontal disease.Subsequent evaluations of the relationship between smoking and these biomarkers revealed a statistically significant increase in TNF-α levels, while the increase in sclerostin levels did not attain statistical significance. However, when the analyses were performed without taking into account age-related effects within groups (adjusted for age), a statistically significant increase in sclerostin levels due to smoking was observed.

Conclusion: In conclusion, it can be posited that the measurement of TNF-α levels in smokers may serve as a biomarker for the diagnosis and progression of the disease. Further studies are required to determine the role of sclerostin in this context.

Keywords: Gingival fluid, Periodontitis, Smoking, Sklerostin, TNF-α

INTRODUCTION

The periodontium consists of gums, periodontal ligament, cementum, and alveolar bone, and the purpose of the periodontium is to ensure the continuity and function of the tooth [1]. Periodontal diseases occur as a result of the disruption of the relationship between the host tissue and microbial plaque. Periodontitis, one of the periodontal diseases, can result in tooth and supporting tissue loss [2].

Local, environmental, systemic, and genetic factors are some of the main factors that play a role in the formation and spread of periodontal disease, especially periodontitis [3]. It is known that smoking is one of the effective environmental risk factors in the formation and progression of periodontal diseases [4].

It is known that the antimicrobial mechanism is impaired in smokers. As a result of impairment in this mechanism, the number of periodontal pathogens increases and the severity of periodontal disease increases accordingly. In addition, it is observed that bone and attachment loss increases in smokers due to the increased release of mediators that cause bone destruction [5].

In smokers; studies are showing increased prevalence and severity of periodontal destruction, pocket depth, attachment loss, and bone loss; Furthermore, suppression of clinical signs of periodontitis has been observed in smokers [6,7].

Although the effects of smoking on host response and its role in increasing the risk of periodontal disease are still being investigated, its effects on innate and acquired immune response cells have been examined separately. Accordingly, it has been reported that cigarette components suppress defense responses of the immune system, but exacerbate pathological responses [8].

Salvi et al. reported that smoking was a risk factor for periodontal diseases and the incidence of periodontitis was 2.5 to 7.0 times higher in smokers [9]. In another study comparing smokers and non-smokers, it was found that the risk of periodontitis was 3.9 times higher in the 19-30 age group and 2.8 times higher in the 31-40 age group [10]. Many studies show that gingivitis is more common in smokers [11,12]. Bergström et al. included smokers and non-smokers with good oral hygiene and similar PI values and found that GI and probing bleeding values were lower in smokers. They explained the reason for this as suppression of the normal inflammatory response against microbial dental plaque (MDP) by smoking [7]. Studies are showing that, in addition to local factors, host-related factors also change the course of periodontal disease [3]. It is thought that host-related factors affect the host tissue response. Biomarkers that are a reflection of the host tissue response, involved in bone metabolism and affecting bone metabolism may be clinical markers that are thought to provide information about the health or disease of periodontal tissues. Sclerostin and TNF-α are among the indicators known to be effective in bone metabolism [13,14].

Main Points

- The search for new biomarkers for the diagnosis of periodontal disease has been widespread in recent years.
- This study aims to demonstrate new biomarkers used in the diagnosis of periodontal disease and to evaluate their effects on smoking.
- It is expected that this study will guide future studies on the biomarkers used in this study.

Sclerostin is a kind of protein known to be cysteine-dependent and encoded by the Sost gene. It is known to be involved in bone metabolism by controlling the differentiation and functions of osteoblasts. It is a protein that inhibits the Wnt/β-catenin signaling pathway while exerting its effects on bone metabolism. It is known to strongly suppress bone growth [15,16]. Sclerostin is elevated in GCF in periodontitis patients [17,18]. There are also animal studies examining the activity of sclerostin in periodontal tissues. One of these studies is a study in which the treatment of bone defects caused by irritation with ligature and periodontitis in animals by applying sclerostin antibody (Scl-ab) was evaluated. In the study, it was observed that alveolar bone healing was significantly improved in the experimental groups treated with Scl-ab. Serum analysis revealed elevated levels of osteocalcin and procollagen type I N propeptide (PINP) in the experimental groups compared to the control groups. This finding indicates the efficacy of Scl-ab in cases involving the coexistence of periodontitis and osteopenia. The study utilised ligature-induced periodontitis in ovariectomised rats, observing that mineral apposition was significantly higher in the Scl-ab-treated group [19,20]. In a study conducted to evaluate sclerostin levels in the gingival groove fluid of patients with periodontitis, it was shown that sclerostin levels were statistically significantly higher in periodontitis patients [21]a glycoprotein, plays a key role in regulating bone mass. In this study, sclerostin levels in the gingival crevicular fluid (GCF. A study in mice has shown that sclerostin deficiency or functional inhibition of sclerostin facilitates bone formation by increasing Wnt/β-catenin signaling, suggesting a direct effect of sclerostin on bone metabolism [22]. TNF-α is one of the main mediators of the immune system. It increases neutrophil activity due to the increased release of matrix metalloproteinases (MMPs) and provides tissue and cell regeneration. It activates osteoclast development and provides

limited tissue repair through increased apoptosis in fibroblasts [23]. High levels of cytokines such as tumor necrosis factor-alpha and IL-1β in infected gingiva and the GCF of patients with periodontitis have revealed that these cytokines may be responsible for periodontal tissue destruction [24,25]. In a study evaluating the effects of receptors inhibiting these cytokines in periodontitis, a 60% decrease in bone resorption and a 67% decrease in osteoclast formation was found [14]. With the increase in gingival inflammation, the amount of TNF-α in GCF also increases. The presence of high levels of TNF-α has a direct effect on the development of periodontitis. This important effect of TNF-α is now known for certain. In many studies, TNF-α antagonist was applied to periodontal disease areas and it was found that the accumulation of inflammatory cells decreased by 80%. It was also found that alveolar bone loss was reduced by 60% in areas with periodontal disease [14,26,27].

Smoking is a well-known significant risk factor in the initiation and progression of periodontal diseases. Studies have demonstrated that sclerostin and TNF-α levels increase in individuals with periodontal diseases. However, the sclerostin level in gingival crevicular fluid and its relationship with clinical parameters in smoking patients with periodontitis has not been examined. In light of the information mentioned above, It is hypothesized that sclerostin and TNF-α levels in gingival fluid will be higher in smoking patients with periodontitis compared to non-smoking patients with periodontitis. This study aims to measure sclerostin and TNF-α levels in periodontally healthy smokers and patients with periodontitis, as well as to assess the association of clinical parameters with smoking.

MATERIALS AND METHODS

Participants and Clinical Evaluations

A total of 72 individuals, comprising 37 males and 35 females, with ages ranging from 23 to 54, who had applied to the Periodontology clinic at Gaziantep University Faculty of Dentistry, were included in this study. The research commenced after the study protocol was meticulously developed and approval was granted by the Gaziantep University Clinical Research Ethics Committee (see Annex-1), under decision number 2019/101 dated 13.03.2019. Before the commencement of the study, all participants were comprehensively informed about the study's objectives and methodology, and they willingly provided their consent by signing the voluntary consent form. All research was conducted according to the Declaration of Helsinki.

Exclusion and Inclusion Criteria

The study excluded individuals who were not between the ages of 18 and 65, pregnant or breastfeeding, had systemic diseases, had parafunctional habits, used antibiotics and oral contraceptives in the previous six months, had periodontal treatment in the previous six months, or had periodontal surgery in the previous six months. The study groups were not comprised of individuals who were using removable prostheses, had any substance addiction (except smoking), had restorative material in the tooth from which the gingival groove fluid sample was taken and in the adjacent teeth, or used a drug that affects periodontal tissues (cyclosporine, phenytoin, etc.). Systemically healthy individuals, who were not pregnant or breastfeeding, who had not undergone periodontal treatment within the previous six months, who had not used antibiotics or oral contraceptives within the previous six months, and who had at least 12 teeth in their mouths, except for third molars, were included in the study groups.

The experimental group comprised 18 individuals who were smokers and 18 who were non-smokers, all of whom were diagnosed with periodontitis following thorough clinical and radiological examinations. They exhibited an average clinical attachment loss of 4 mm or more, as well as a Probing Pocket Depth of 5 mm or more in at least 20 regions within the oral cavity. The control group consisted of 36 individuals who had overall periodontal health, with an equal distribution of 18 smokers and 18 non-smokers.

Within the smoker group, individuals who smoked a minimum of 10 cigarettes per day were assessed, while in the non-smoker group, participants who had never smoked in their lifetime or had abstained from smoking for at least two years were included. Smoking status was determined through direct inquiry with each individual [28,29].

Group A: Non-smoking periodontal healthy individuals (18 individuals, 8 males, and 10 females, aged between 27-46 [30].
Group B: Non-smoking individuals with periodontitis (18 individuals, 11 males and 7 females, aged between 29-51) Stage-3/4 degree A [30].

Group C: Periodontal healthy individuals who smoke (18 individuals, 9 males, and 9 females, aged between 23-54) [30].
Group D: Periodontitis individuals who smoke (18 individuals, 9 males, and 9 females, aged between 29-51) stage 4 degree C [30].

Clinical Parameters

Before collecting GCF samples, clinical measurements were conducted to assess the patients' periodontal status. The Williams (Williams, Hu-Friedy, Chicago, IL) probe was employed to make clinical measurements. During the clinical examination, several measurements were taken to evaluate the patients' periodontal health, including PI, PPD, GI, CAL, and bleeding on probing (BOP) [31–33]. PI, GI, and BOP were measured on four different surfaces of each tooth, encompassing the mesiobuccal, mid-buccal, distobuccal, and mid-palatal/lingual regions. These measurements were used to assess the patients' oral hygiene and gingival health. PPD and CAL measurements were taken from six different surfaces of each tooth. These surfaces included the mesio-buccal, mid-buccal, disto-buccal, mesiolingual/palatal, mid-lingual/palatal, and distolingual/palatal regions of the tooth. These measurements were utilized to evaluate the condition of the periodontal attachment and provide a more detailed assessment of periodontal health. These clinical measurements formed the foundation of this study and assisted in determining the patients' periodontal health status. The clinical measurements and collection of GCF samples were conducted by a single physician.

Collection of GCF Samples

Gingival crevicular fluid (GCF) samples were collected 24 hours after the periodontal clinical measurements of the patients. GCF samples were obtained from two sites during a single session, selected from the tooth in each quarter of the jaw with the highest probing pocket depth. Sterilized paper strips were used for GCF sample collection. Before sampling, the target areas were isolated using cotton tampons, and any plaque in these areas was removed with a probe. The areas were then meticulously dried using air spray, and applied from both the vestibular and palatinal regions, perpendicular to the tooth's long axis, to prevent saliva contamination. Each paper strip (Periopaper®, OraFlow Inc., Plainview, New York, USA) was gently placed into the gingival pocket until slight resistance was encountered (Utilizing the Brill Technique)[34] and left in the pocket for 30 seconds. Samples contaminated with blood or saliva were excluded from the evaluation. The volume of GCF on the strips was measured and recorded using a pre-calibrated Periotron 8000. The GCF volume was then converted to microliters (µl)[35]. This conversion was performed by transmitting the Periotron 8000 measurement values to a computer via a serial connection using the PERIOTRON (Orafow Inc., Plainview, New York, USA) program. After each volume determination, the device's poles were wiped with a dry gauze to prevent liquid contamination. Paper strips containing GCF samples were placed in Eppendorf tubes and stored at -80 degrees Celsius until the day of analysis.

Measurements of GCF Sclerostin, and TNF-α Levels

The sclerostin and TNF-α reagents, as well as the microplates containing GCF samples reserved for the study, were allowed to reach room temperature. Sclerostin and TNF-α levels in the GCF samples were measured using an ELISA method and Finetest ELISA kits (Finetest Sklerostine kit Batch No:H0599E108 E / FineTest TNF-α kit Batch No:H0302E108 E). These kits are based on the principle of a sandwich enzyme-linked immunosorbent assay. Measurement of sclerostin and TNF-α was performed with an ELISA reader (Biotek, ELx800, USA) at 450 nm. Sclerostin and TNF-α levels for both patients and controls were calculated with the assistance of a standard graph.

Statistical Analysis

The conformity of the data to a normal distribution was assessed using the Shapiro-Wilk test. For comparing non-normally distributed characteristics among more than two independent groups, Kruskal-Wallis and Dunn multiple comparison tests were employed. The Chi-square test was used to examine relationships between categorical variables, while the Spearman rank correlation coefficient was used to assess relationships between numerical variables. A linear mixed-effects model was employed to analyze SOST and TNF-α values, with age as a controlled variable. Statistical analyses were conducted using the SPSS for Windows version 22.0 software package, and a significance level of $P<0.05$ was considered statistically significant.

The minimum number of patients required in each group was determined to be 17 ($\alpha=0.05$, $1-\beta=0.80$) to detect a significant difference between the smoking and non-smoking groups concerning sclerostin and TNF-α values, with a Cohen's d effect size of 1.00. The analysis was performed using G Power version 3.1.

RESULTS

Demographic Findings

A total of 72 volunteers, 37 males and 35 females aged 23-54 years, were included in this study. Non-smoking periodontally healthy individuals were defined as "Group A" (n;18), non-smoking periodontally healthy individuals were defined as

"Group B" (n;18), smoking periodontally healthy individuals were defined as "Group C" (n;18), and smoking periodontally healthy individuals were defined as "Group D" (n;18). Among the individuals who participated in the study, 10 of the individuals in Group A were female and 8 were male; 7 of the individuals in Group B were female and 11 were male; 9 of the individuals in Groups C and D were female and 9 were male. The comparison of the demographic data of the individuals in the study between the groups is shown in Table 1.

The mean age ± standard deviation of the participants was 37.51±11.21 years. When the age medians were examined, a statistically significant difference was observed between the non-smoking healthy group and the smoking periodontitis (A and D) groups, but no statistically significant difference was found between all other groups. The groups were balanced in terms of gender distribution (P=0.788) (Chi-square test)

Clinical Periodontal and Biochemical Findings

Table 2 shows the intergroup changes and comparisons of clinical and laboratory findings including clinical data of the sample area (PI, GI, PPD), whole mouth kinetic data (PI(t), GI(t), PPD(t), CAL(t),), GCF volume measurements and GCF sclerostin and TNF-α levels.

According to the results of statistical analysis, whole mouth PI(t), PPD(t), GI(t), and CAL(t) values were found to be statistically significantly higher in the periodontitis group (B and D) than in the healthy group (A and C) ($p<0.001$). There was no statistically significant difference in whole mouth PI(t), PPD(t), and CAL(t) values between smoker periodontitis and non-smoker periodontitis groups (B and D). There was a statistically significant result in GI(t) values between smoker periodontitis and non-smoker periodontitis groups (B and D). ($p=0,015$).

There was no statistically significant difference in whole mouth GI(t), PPD(t) values between healthy smokers and healthy non-smokers (A and C). Statistically significant results were found in whole mouth PI(t), CAL(t) values between healthy smokers and healthy non-smokers (A and C) ($p<0,005$).

When the sample site PI, PPD, and GI values were analyzed, it was found that they were statistically significantly higher in the periodontitis group (B and D) than in the healthy group (A and C) ($p<0.001$). There was no statistically significant difference in sample site PI, PPD, and GI values between periodontitis smokers and non-smokers (B and D) and between healthy smokers and healthy non-smokers (A and C).

When GCF volume (µl) was analyzed, it was found that the mean GCF volume was statistically significantly higher in the periodontitis group (B and D) compared to the healthy group (A and C) ($p<0.001$) (Figure 1). There was no statistically significant difference in GCF volume (µl) between periodontitis smokers and non-smokers (B and D) and between healthy smokers and healthy non-smokers (A and C).

When the total amount of GCF sclerostin was evaluated, it was observed that the sclerostin values of the periodontitis group (B and D) were higher than the healthy group (A and C), and the participants in the smoking groups (C and D) were higher than the participants in the non-smoking groups (A and B), but the difference was not statistically significant.

When examining the age of the participants, a statistically significant difference was observed between the non-smoking healthy group and the smoking periodontitis (A and D) groups ($p<0.005$). When the group and age were included in the Mixed effect linear model to evaluate the factors affecting the sclerostin values, statistically significant results were found between the non-smoking healthy and smoking periodontitis (A and D) and non-smoking and smoking periodontitis (B and D) Groups. ($p<0,005$) (Figure 2) (Table 3)

When the total amounts of GCF TNF-α were evaluated, it was seen that the participants in the smoking groups (C and D) were higher than the participants in the non-smoking groups (A and B); TNF-α values of individuals with periodontitis were statistically significantly higher than healthy individuals. ($p<0.005$). When non-smoking healthy and smoking health groups were compared (A and C), it was observed that the GCF TNF-α values of smoking individuals were statistically significantly higher ($p<0.005$). In the comparison of non-smoking healthy and smoking periodontitis group (A and D), GCF TNF-α values of smokers with periodontitis were statistically significantly higher ($p<0.001$). In the comparison of smoker periodontitis and non-smoker periodontitis groups (B and D), GCF TNF-α levels of smoker periodontitis individuals were statistically significantly higher ($p<0,005$) (Figure 3).

Table 1. Comparison of demographic data between groups

		A (N=18) α	B (N=20) β	C (N=20) γ	D (N=20) Δ	Total	P
Age †		35,28 ± 6,2	37,5 ± 7,5	37,56±7,74	41,44±5,46	37,94±6,72	* αδ,
Min/Max		27/46	29/51	23/54	29/51	23/54	
Gender Ω	**M**	8 (44,4)	11 (61,1)	9(50)	9 (50)	37 (51)	
	W	10(55,6)	7 (38,9)	9(50)	9 (50)	35 (49)	

A (α): Non-smoker periodontally healthy group, B (β): Non-smoker periodontitis group, C (γ): Smoker periodontally healthy group, D (δ): Smoker periodontitis group

† mean ± std.deviation M:male W: Female

Ω n (%)

*Statistically significant ($p<0.05$)

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

Table 2. Clinical periodontal parameters of all groups

	A (N=18) α	B (N=18) B	C (N=18) Γ	D (N=18) δ	P
PI(t)†	0,74±0,09	2,3 ±0,2	0,89 ± 0,05	2,32 ± 0,2	** αδ,βγ, γδ,αβ *αγ
PPD(t)(mm)†	2,32±0,42	6,35 ± 1,15	2,32 ± 0,11	6,84 ± 0,71	** αβ, αδ,βγ, γδ
GI(t)†	0,43±0,21	1,94 ± 0,11	0,24±0,12	1,61 ± 0,13	**γδ, βγ, αδ, αβ *βδ
CAL(t)(mm)†	0,11±0,13	7,07 ± 0,77	0,38 ±0,24	7,4 ± 0,83	** αβ, αδ, βγ, γδ *αγ
PI†	0,39 ± 0,5	1,83 ± 0,38	0,22±0,43	1,72 ± 0,46	** γδ, βγ, αδ,αβ
PPD(mm)†	2,67±0,59	6,5 ± 1,04	2,56±0,51	7,44 ± 0,98	**βγ, γδ,αβ,αδ
GI †	0,11±0,32	1,72 ± 0,46	0,17±0,38	1,44 ± 0,51	** αδ, αβ, γδ, Bγ
CAL (mm)†	0	6,72± 0,57	0	7,2± 0,64	** αβ, αδ, βγ, γδ *αγ
GCF Volüme (µl)†	0,36±0,11	1,13 ± 0,91	0,27±0,11	0,8 ± 0,17	** βγ, γδ, αβ,αδ
Sklerostin (ng/mL)†	29,57±6,23	30,63±4,95	34,43±8,16	39,29 ± 13,75	N
TNF-α (ng/mL)†	13,78 ± 5,18	14,51 ± 7,3	19,79 ± 9,12	24,91 ± 11,33	** αδ * αγ, βδ

A (α): Non-smoker periodontally healthy group, B (β): Non-smoker periodontitis group, C (γ): Smoker periodontally healthy group, D (δ): Smoker periodontitis group

CAL: Clinic attachment level PI(t):Plaque index total, PPD(t): Probing pocket depth total, GI(t): Gingival index total, CAL(t): Clinical attachment level total, PI: Plaque index sample site, PPD: Probing pocket depth sample site, GI: Gingival index sample site, GCF: Gingival Clevicular Fluid

† mean ± std.deviation

* Statistically significant ($p<0.05$)

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

N: no statistically significant result

Table 3. Results when group and age are included in the mixed effect linear model (Adjusted by age)

Parameter	Prediction	standard deviation	P	%95 confidence interval	
				lower limit	upper limit
A vs D	-9,43	3,16	0,004*	-15,73	-3,13
B vs D	-8,47	3,06	0,007*	-14,59	-2,36
C vs D	-4,68	3,06	0,131	-10,79	1,43
Yaş	0,05	0,16	0,766	-0,27	0,37

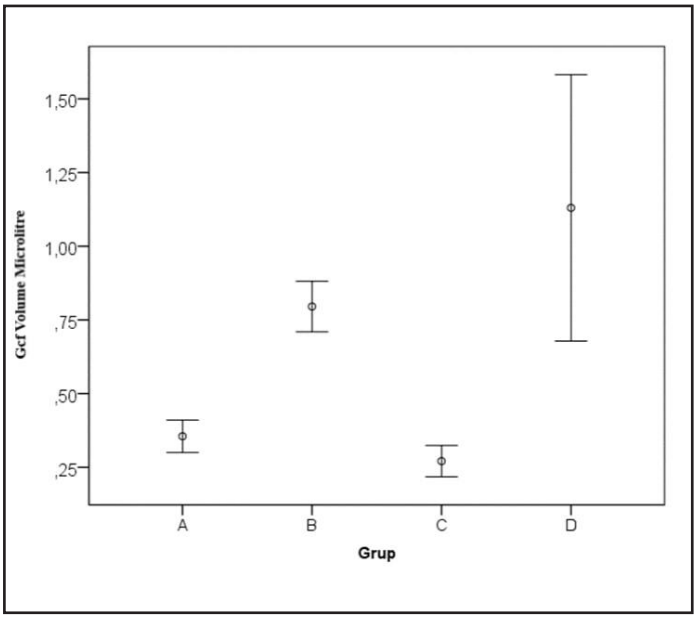

Figure 1. GCF volume (µl) values of the groups

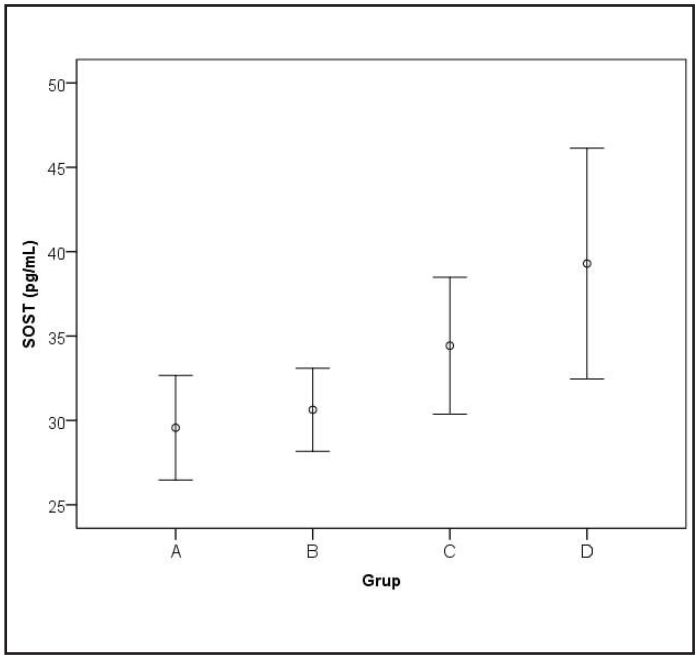

Figure 2. GCF TNF-α levels of the groups

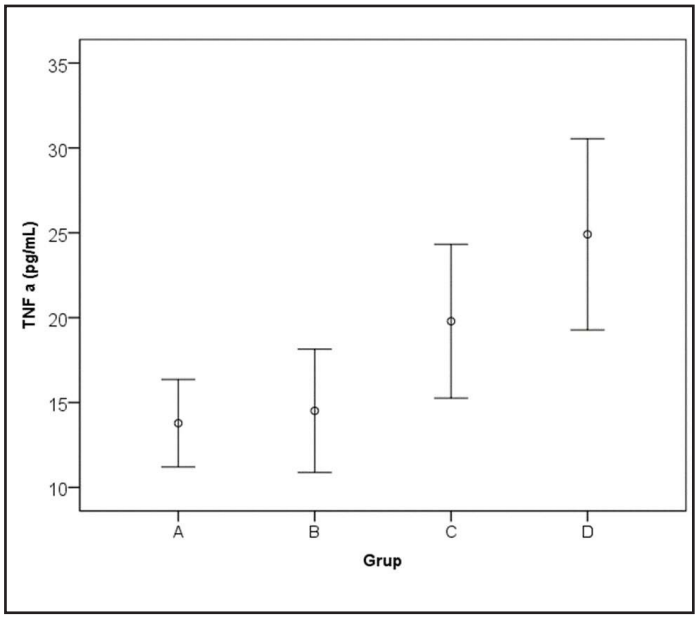

Figure 3. GCF sclerostin levels of the groups

DISCUSSION

Risk factors are as important as bacteria and the host tissue defense system in the initiation and progression of periodontal disease [5,36]. Numerous studies have examined the impact of smoking, one of the environmental risk factors, on periodontal tissues and periodontal diseases [7]. It is believed that antimicrobial defense mechanisms are impaired in smokers, leading to an increase in the number of pathogens, which in turn exacerbates the destruction and impact of periodontal disease [5,37,38]. In this study, conducted at Gaziantep University, Faculty of Dentistry, Department of Periodontology, a total of 72 individuals, 37 males and 35 females, aged between 23 and 54 years, were included. Among these, 36 patients were periodontally healthy and 36 were periodontitis patients. Patient selection was performed according to inclusion and exclusion criteria to support the diagnosis. By selecting patients following these criteria, we aimed to control parameters that might affect the study results and achieve standardization between the groups.

Following a thorough evaluation of the study's findings, it was ascertained that the sclerostin and TNF-α values were elevated in individuals diagnosed with periodontitis in comparison to those categorized as healthy. These observations signify the potential of these markers as diagnostic biomarkers for periodontal disease. Furthermore, the study revealed that individuals with periodontitis who smoke exhibited higher levels of sclerostin and TNF-α compared to non-smokers within the same group. This increase was found to be statistically significant for TNF-α, but not for sclerostin.

The study highlights the role of TNF-α as a critical inflammatory marker in periodontitis, with elevated levels observed in individuals with the disease compared to healthy controls. Notably, the highest TNF-α levels were detected in periodontitis patients who smoked, underscoring the exacerbating effect of smoking on periodontal inflammation. Furthermore, the analysis using linear mixed-effects modeling, which accounted for the variability in age distribution among the groups, identified a significant difference in sclerostin levels between non-smoker and smoker periodontitis groups. This suggests that smoking may influence sclerostin expression, potentially contributing to the pathophysiology of periodontitis in smokers. However, the Kruskal-Wallis test, applied to assess non-normally distributed data across multiple groups, did not show statistically significant differences in sclerostin levels, indicating that the relationship between sclerostin and periodontal disease may be more complex and influenced by factors beyond smoking status. These findings suggest that while TNF-α and sclerostin are relevant biomarkers in periodontitis, their interactions and influences are nuanced, particularly in the context of smoking, and warrant further investigation.

In the biochemical analyses performed in this study, it was observed that sclerostin values were higher in healthy smokers and smokers with periodontitis compared to non-smokers, though the difference was not statistically significant. Since the age distribution between the groups was not balanced, linear mixed effect modeling was used to compare the sclerostin and TNF-α values of the smoker periodontitis group and the other groups, adjusting for age. This analysis revealed that sclerostin levels in the smoker periodontitis group were significantly higher than those in the non-smoker periodontitis group. Additionally, sclerostin levels in the smoking periodontitis group were significantly higher compared to the non-smoking healthy group. These findings suggest that the apparent differences in sclerostin levels are not solely due to age distribution among individuals. Increasing the number of patients in future studies with more homogeneous groups could yield results that further support our hypothesis. This study also found that TNF-α levels were significantly higher in the healthy smoker group compared to the healthy non-smoker group.

A study conducted by Georgios et al. (2019) demonstrated the presence of the levels of sclerostin, WNT-5a, and TNF-α in the GCF of patients with and without periodontitis. WNT-5a gingival protein levels showed high diagnostic value for diffuse moderate to severe chronic periodontitis, while exhibiting low accuracy for localized chronic periodontitis [39].

TNF-α and IL-1b are known to induce SOST expression [40,41]. Baek et al. reported that TNF-α, a transcription activator for sclerostin, induces the synthesis of sclerostin in MLO-Y4 osteocytes. It was also demonstrated that the nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) directly binds to the NF-kB binding elements on the mouse SOST promoter. Therefore, the synthesis of sclerostin is upregulated due to NF-kB activation [42].

The study by Ashifa N et al. demonstrated that GCF sclerostin levels were elevated in patients with periodontitis in comparison to those with gingivally healthy periodontal conditions. Furthermore, the findings supported the hypothesis that this could be regarded as a potential biomarker of disease activity [21]a glycoprotein, plays a key role in regulating bone mass. In this study, sclerostin levels in the gingival crevicular fluid (GCF. In the study conducted by Ren Y et al., the SOST gene was removed in mice, effectively halting the synthesis of sclerostin. It was observed that the incidence of bone destruction was reduced, while bone formation was enhanced in mice where sclerostin synthesis was terminated. The hypothesis that osteocyte pathological alterations and sclerostin production from these cells are linked to periodontal defects has been substantiate [43]. With the increase in gingival inflammation, the amount of TNF-α in the GCF also increases and the presence of high levels of TNF-α has a direct effect on the formation of periodontitis. This important effect of TNF-α has been confirmed just like the effects of IL-1β and many studies have shown that the accumulation of inflammatory cells is reduced by 80% and alveolar bone loss is reduced by 60% in periodontal disease areas treated with tumor necrosis factor-alpha and IL-1β antagonists [26,27].

Moreover, TNF-α levels were higher in periodontitis smokers than in non-smoker periodontitis patients. These differences suggest that smoking increases the amount of mediators that initiate inflammation. The biochemical and statistical analyses demonstrated that smoking elevates the levels of TNF-α, a known pro-inflammatory mediator, and sclerostin, a strong suppressor of bone growth. While the difference in TNF-α levels was statistically significant, the significance in sclerostin levels was less pronounced, possibly due to the smaller sample size and unequal age distribution.

When the results of this study were evaluated, it was seen that the sclerostin levels of the periodontitis group were higher than the healthy group, but not statistically significant. Statistically significant results ($p<0.005$) were found between healthy non-smoker and smoker periodontitis (A and D) and healthy non-smoker and smoker periodontitis (B and D) groups. This data tells us that our hypothesis is statistically significant if the age distribution of the groups is more equal. The fact that the number of samples taken was close to the minimum value of the power analysis suggests the possibility of strengthening the results of the study with a larger number of samples.

In this study, the Brill technique was used during the collection of gingival groove fluid samples [34]. When other studies in the literature are examined, it is seen that samples are collected with similar techniques [44,45].

The assessment of smoking status was conducted through the utilisation of an individual questioning method. In this method, the responses provided verbally by the samples are of the utmost importance. While the individual questioning method is considered to be a safe approach, this particular situation does, however, present a limitation to the study [29]. This study has several limitations that may influence the generalizability of its findings. First, the small sample size and uneven age distribution among groups may have affected the statistical power of the analysis, particularly concerning sclerostin levels. Additionally, smoking status was assessed using self-reported data, which may be subject to reporting bias and inaccuracies. The study also relied on the Brill technique for GCF sample collection, which, while widely used, may have inherent variability in sample handling and processing. Finally, the cross-sectional design of the study limits its ability to infer causation between smoking, sclerostin levels, and periodontal disease progression. Future studies with larger, more demographically homogeneous samples and objective smoking verification methods are needed to address these limitations.

CONCLUSION

The findings of this study underscore the significant impact of smoking on periodontal inflammation and bone destruction, as evidenced by elevated levels of TNF-α and sclerostin in smokers with periodontitis. While the association between TNF-α and smoking was statistically significant, the relationship between sclerostin and smoking, though apparent, requires further investigation due to the small sample size and demographic imbalances. These results highlight the potential of sclerostin as a biomarker for periodontal disease activity, particularly in smokers. Further research with larger, well-balanced cohorts is essential to elucidate the complex interactions between smoking, sclerostin, and periodontal pathology. Addressing these gaps could provide valuable insights into targeted therapeutic strategies for smoking-related periodontal diseases.

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Informed Consent: Informed Consent has been obtained.

Ethical Approval: Gaziantep University Clinical Research Ethics Committee, 13.03.2019 - 2019/101.

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Original Research

The Role of Artificial Intelligence in Radiology Residency Training: A National Survey Study

Emre Emekli[1,2,*], Özlem Coşkun[3], Işıl İrem Budakoğlu[3]

[1] Department of Radiology, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Türkiye
[2] Department of Medical Education, Gazi University, Institute of HealthSciences, Ankara, Türkiye
[3] Department of Medical Education and Informatics, Gazi University, Faculty of Medicine, Ankara, Türkiye

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Corresponding Author
Emre Emekli, Assist. Prof. MD
Address: Department of Radiology, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Türkiye
E-mail: emreemekli90@gmail.com

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ABSTRACT

Objective: Artificial Intelligence (AI) offers opportunities for radiologists to enhance workflow efficiency, perform faster and repeatable segmentation, and detect lesions more easily. The aim of this study is to investigate the current knowledge and general attitudes of radiology resident physicians towards AI. Additionally, it seeks to assess the current state of AI/ML/DL education in radiology residency, the awareness and use of available educational resources.

Methods: A cross-sectional study was conducted using an online survey from October 2023 to February 2024. The survey included demographic data, AI knowledge, attitudes towards AI, and the role of AI in medical education. Survey questions were developed based on literature and reviewed by experts in medical education and radiology.

Results: The study included 155 participants (38.7% female) with an average age of 28.81±4.77 years. About 80.6% were aware of AI terms, with a mean knowledge score of 3.02±1.39 on a 7-point Likert scale. Most participants (90.3%) had no programming knowledge. Only 22.6% used AI tools occasionally. The majority (73.4%) believed AI would change radiology's future, though only 10.3% felt radiologists' jobs were at risk. Regarding AI education, 84.5% reported no formal training, and awareness of online resources was low.

Conclusion: The study found that while awareness of AI among radiology residents is high, their knowledge and practical use of AI tools are limited. AI education is largely absent from residency programs, and awareness of online educational resources is low. These findings highlight the need for integrating AI training into radiology education and increasing awareness of available resources.

Keywords: Artificial Intelligence, Radiology, Medical Education

INTRODUCTION

Deep Learning (DL) and Machine Learning (ML), which are generally part of Artificial Intelligence (AI) algorithms, have shown promising performance when applied to medical imaging techniques [1,2]. AI offers opportunities for radiologists to make their workflow more efficient, perform faster and repeatable

segmentation, and detect lesions more easily [3]. Although these advancements are progressing rapidly, their integration into routine workflows is not happening at the same pace. Currently, most studies are presented at scientific meetings like conferences and at an academic level. Clinically, it can be said that the adoption of AI tools in practical operations is still in its early stages [4,5]. In the face of these changes in AI, the literature and, more frequently, the media often highlight its negative aspects, leading medical students, interns, and even radiologists in some cases to fear that their roles might be taken over by AI [6].

Alongside these developments, the popularity of Large Language Models (LLMs) developed in the last two years has significantly increased, and they have become frequently used in our lives. LLMs, using DL, have the ability to understand, generate, and interact with human language. Their success continues to grow day by day [7]. There are many studies conducted in the field of radiology as well. Primarily, it is said that LLMs assist radiologists in learning and education, optimizing and simplifying tasks, and aiding with non-interpretative tasks [8,9]. Considering all these developments, AI, LLM, DL, and ML are increasingly showing their impact in radiology, as in all fields. With the increasing integration of AI, interest in including AI education in radiology curricula is also growing. Therefore, various national and international resources are provided for education [10,11].

The aim of this study is to investigate the current knowledge and general attitudes of radiology resident physicians towards AI. Secondly, it aims to assess the current state of AI/ML/DL education in radiology specialty training, evaluate the awareness and use of provided educational resources by residents, and understand the residents' perspectives on the scope of AI education and their preferred learning methods/tools.

Main Points

- Radiology residents have high awareness of AI terms, but their knowledge levels and practical use of AI tools are limited.
- AI education is largely absent in radiology residency programs, with most participants reporting no formal training or awareness of educational resources.
- The majority of participants view AI as a tool that will transform radiology rather than a threat to radiologists' jobs.
- Findings highlight the need to incorporate AI training into residency curricula and improve awareness of available educational resources.

MATERIALS AND METHODS

Ethical approval was obtained from the Gazi University Ethics Committee (Date 03.10.2023/No: 2023 – 1171). The study was conducted cross-sectionally using an online survey form created via Google Forms. Data collection took place between October 2023 and February 2024. The survey included an informed consent form that provided brief information about the study and explained its purpose. The survey consisted of four main sections: demographic data, AI knowledge, attitudes towards AI, and the role of AI in medical specialty training.

The survey form was developed by two individuals considering literature data related to AI in radiology: a medical doctor with a Ph.D. in medical education and a radiology specialist medical doctor who is a Ph.D. student in medical education. The survey questions were then reviewed and finalized by another faculty member working in medical education. The survey form was prepared in Turkish.

The survey inquired about the inclusion of AI in radiology residency training and participants' knowledge levels on AI/ML/DL topics using a 7-point Likert scale (1 = very poor / definitely should not be included, 7 = very good / definitely should be included). The survey was distributed to members via email through the Turkish Society of Radiology.

RESULTS

Participant Data

The study included 155 participants who consented to take part. The average age of the participants was 28.81±4.77 years, with 94 (60.6%) being male, 60 (38.7%) female, and one person (0.6%) not specifying their gender. The years of specialty training and institutions of the participating resident physicians are presented in Table 1.

AI Knowledge and Usage

Out of the participants, 125 (80.6%) reported being aware of AI/ML/DL terms. When asked to rate their knowledge levels on a 7-point Likert scale, the average score was 3.02±1.39, indicating a moderate level of knowledge. A total of 140 participants

(90.3%) stated they had no programming knowledge, while 15 participants (9.7%) reported having basic programming knowledge.

Regarding the use of AI/ML/DL tools, 120 resident physicians (77.4%) said they never used these tools, 7 (4.5%) used them a few times, 2 (1.3%) used them daily, 7 (4.5%) used them weekly, and 19 (12.3%) used them monthly. When asked about the usage of AI tools in their institutions, 88 (56.8%) said they were not used, 28 (18.1%) said they were used, and 39 (25.2%) did not know.

Attitudes Towards AI

When asked if AI would change the future of radiology, 114 participants (73.4%) answered yes, 5 (3.2%) answered no, and 36 (23.2%) answered maybe. Of those who responded yes or maybe, 12 (7.7%) believed this change would occur in less than five years, 78 (50.3%) in 5-10 years, 43 (27.7%) in 10-20 years, and 17 (11%) in more than 20 years.

Regarding whether they thought radiologists' jobs were at risk due to AI, 16 participants (10.3%) answered yes, 94 (60.6%) answered no, and 45 (29%) answered maybe. The reasons why resident physicians did or did not consider radiologists' jobs at risk are detailed in Table 2.

AI Education

The presence of faculty members specializing in AI and participation in any research related to AI at the institutions is summarized in Table 3. When asked whether AI should be part of radiology education, the average response on a 7-point Likert scale was 5.09 ± 1.72, indicating a strong desire for AI to be included in the curriculum.

Regarding AI-related resources, 131 participants (84.5%) reported that no resources were provided, 3 (1.9%) mentioned classroom lectures, 4 (2.6%) noted online materials, 1 (0.6%) attended a national-level lecture, 7 (4.5%) participated in a national congress/seminar, and 2 (1.3%) received institutional training. The duration of this training was less than 1 hour for 3 participants (1.9%) and between 1-5 hours for 7 participants (4.5%). A total of 142 participants (91.6%) stated that they did not receive any AI education outside their institutions. Of those who did, 10 received 1-5 hours of training.

When asked about their awareness of various AI educational resources, such as the ESR AI blog, ESR "Masterclass in AI" courses, RSNA AI videos, Radiology: Artificial Intelligence Journal, "AI Journal Club" managed by the ACR-Resident and Fellow section, and the ACR Data Science Institute/AI Lab, 119 participants (76.8%) reported being unaware of any of these resources.

Table 1. Years of Residency in Radiology and Institutions of Participants

Years of Residency in Radiology	**Number (n)**	**Percentage (%)**
1	43	27.7
2	49	31.6
3	25	16.1
4	18	11.6
5	20	12.9
Institution	**Number (n)**	**Percentage (%)**
University (State)	112	72.3
Ministry of Health Training Hospital	40	25.8
University (Private)	3	1.94
Number of Residents in the Institution	**Number (n)**	**Percentage (%)**
Less than 10	4	
Between 10-20	58	
Between 20-30	28	
Between 30-40	34	
More than 40	31	

Table 2. Participants' Opinions on the Impact of AI on the Future of Radiology

Reason It's at Risk (n=87)	Number (n)	Percentage (%)	Reason It's Not at Risk (n=120)	Number (n)	Percentage (%)
The number of radiologists needed will decrease with the use of AI.	23	26.44	The role of radiologists does not change with AI; it may even make their work easier.	60	50
AI tools will perform tasks such as image interpretation/comparison more efficiently, reducing the need for radiologists.	40	45.98	The role of radiologists may change, but AI cannot replace them.	60	50
The cost-effectiveness of AI will make it attractive for institutions, leading to the replacement of radiologists.	24	27.59			

Table 3. Status of Academic Interested with AI and Opinions on AI as a Sub-discipline

	Yes n (%)	No n (%)	Don't Know / Not Sure n (%)
Are there faculty members in your department interested AI in radiology?	51 (32.9)	48 (31)	56 (36.1)
Have you participated in any research related to AI/ML/DL?	19 (12.3)	136 (87.7)	
Do you think imaging informatics/AI should be a sub-specialty in radiology?	57 (36.8)	33 (21.3)	65 (41.9)

DISCUSSION

When evaluating participants' knowledge and attitudes towards AI, 80.6% reported being aware of AI terms. Similar rates have been found in literature [12]. When asked about their knowledge levels, participants were assessed to have a moderate level of understanding. Literature also indicates that radiologists generally have basic to intermediate knowledge of AI [13]. In this study, 90.3% of participants reported having no programming knowledge, whereas a study by Salastekar et al. found this rate to be 75%. Thus, radiology resident physicians in this study appear to have a comparable level of basic AI knowledge to those reported in the literature.

In the literature, a study reports that 39% of radiologists experience fear related to AI [12]. In this study, 60.6% of participants stated that radiologists' jobs are not at risk due to AI, while 29% thought they might be at risk. The same study indicated that fear of AI was higher among those with less AI knowledge [12]. As AI knowledge and usage increase rapidly over time, it is possible that the fear of AI may decrease.

In this study, participants strongly expressed the need for AI education to be included in specialty training. In the United States, studies by Salastekar et al. and Huisman et al. found that 83% and 79% of respondents, respectively, believed that AI should be part of radiology residency training [14,15]. Similar rates have been reported in studies from Singapore (84.8%) and Spain (92.9%) [16,17]. There appears to be a global consensus on the necessity of including AI education in specialty training programs.

Studies in the United States indicate that the inclusion of AI in specialty training curricula varies between 25% and 50% [16,18]. In this study, 84.5% of participants reported that no resources were provided for AI education. Compared to the literature, the rate of AI education provision in our country is found to be very low. Additionally, 76.8% of participants in this study stated that they were not aware of online AI resources. Similar findings in the literature indicate a lack of awareness of online resources among radiology residents [14]. Regarding the use of AI tools, 77.4% of participants reported never using any AI tools personally, and 56.8% stated that AI tools were not used in their institutions, with 25.2% not knowing about their usage status. In the literature, it is seen that the utilization rates reported in the survey studies are quite high compared to this study [19,20]. When evaluating AI education and usage in institutions, this study suggests that AI education is not adequately provided in radiology specialty training in our country, and awareness of existing online resources is low. Additionally, the usage rates of AI tools in institutions are currently low.

This study has some limitations. First, being a cross-sectional study, it cannot be generalized to the entire population. Second, given the rapidly changing and evolving nature of AI tools, the current findings may have already shifted. Third, the sample size is relatively small. However, efforts were made to distribute the survey nationwide, ensuring participation from various institutions.

CONCLUSION

Compared to the literature, this study found that participants were similarly aware of AI, but their knowledge levels and basic understanding were low. These findings are consistent with literature data. However, when evaluating specialty training, it was found that most institutions do not provide AI-related education, and many participants are not aware of online resources. Therefore, this study is important for highlighting the deficiencies in the education of the radiology department, where technology plays a significant role. It also serves as a needs analysis for future training and the creation of national AI resources.

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Author Contribution: EE: Conception, Design, Materials, Data Collection, Analysis, Literature Review, Writing, Critical Review.
ÖC: Materials, Data Collection, Literature Review.
İİB: Materials, Data Collection, Literature Review, Supervision.

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Original Research

Investigation of the Effectiveness of Nutrition at the Molecular Level in Patients with Sepsis

Hamit Yıldız[1,*], Türkay Güncü[2]

[1] Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
[2] SANOVEL İlaç AS., Istanbul, Turkiye

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Corresponding Author
Hamit Yildiz, MD, PhD
Address: SANOVEL ILAC AS, Istanbul, Türkiye
E-mail: turkayguncu@hotmail.com

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ABSTRACT

Objective: The aim of this study was to compare inflammatory and anti-inflammatory molecule levels in sepsis patients receiving normal (1.3 mg/kg/day) and high (2 mg/kg/day) protein supplementation.

Methods: Two groups of patients were compared based on protein supplementation: normal (1.3 mg/kg/day) and high (2 mg/kg/day). Levels of kallistatin, nesfatin-1, plasminogen activator inhibitor-1 (PAI-1), and high mobility group box-1 (HMGB-1) were measured. Disease severity was assessed using APACHE II, SAPS, and SOFA scores.

Results: Demographic characteristics and intensive care scores were similar between groups ($p>0.05$). Group 1 had significantly higher 0-hour levels of HMGB-1, kallistatin, PAI-1, and nesfatin-1 compared to 24 and 48 hours ($p<0.001$). Group 2 had higher 0-hour levels, but changes were not significant ($p>0.05$)

Conclusions: High-dose protein feeding in sepsis patients may not suppress inflammation-related protein synthesis despite the presence of oxidative damage and muscle catabolism.

Keywords: Sepsis, Biomarker, Kallistatin, Plasminogen Activator Inhibitor-1, Nesfatin-1, High Mobility Group Box-1, protein diet

INTRODUCTION

Sepsis is a syndrome accompanied by physiological, pathological and biochemical abnormalities induced by infection and is a serious public health problem. Although its true incidence is unknown, it is estimated to be one of the leading causes of mortality worldwide [1].

Septic shock is a condition characterized by a mortality risk much higher than sepsis alone, accompanied by circulatory system disorders, cellular and metabolic abnormalities, the need for vasopressors to maintain mean arterial pressure at or above 65 mmHg, and a serum lactate level above 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. In the presence of these two findings, the mortality risk is higher than 40% [1].

Sepsis and related status septic shock have high mortality rates ranging from 20% to 50% even today. Although it is necessary to determine the causative microorganism, culture tests are not always useful due to their time-consuming and low sensitivity [2].

The SOFA and APACHE 2 scores are frequently used to assess the severity of sepsis. The use of these scoring systems is quite complex and time-consuming. It may not always be possible to collect the parameters required for scoring. Therefore, a biomarker that can be easily measured is needed to more easily assess the severity of sepsis [2].

Malnutrition, especially sepsis, is associated with increased morbidity and mortality in intensive care patients, and nutritional support is extremely important in the standard care of these patients. Sepsis is characterized by proinflammatory metabolic response, increased energy consumption, accelerated catabolism, and hyperdynamic circulatory changes. In this context, a decrease in lean body mass, organ function, and immune function deterioration occur in sepsis patients, and if this condition persists for a long time, conditions such as protein energy malnutrition, increased infectious morbidity, artificial respiration dependency, increased intensive care and hospital stay, and increased mortality may occur.

The aim of this study was to compare the levels of inflammatory and anti-inflammatory molecules in patients with sepsis who were fed 1.3 mg/kg/day protein supplementation and 2 mg/kg/day protein supplementation.

MATERIAL AND METHODS

The study was initiated by the Gaziantep University Faculty of Medicine Clinical Research Board with the decision number 178 dated 08.05.2019. This study was supported by Gaziantep University Scientific Research Projects with the project number TF.UT.19.20. The study was conducted prospectively with sepsis patients admitted to the Gaziantep University Faculty of Medicine, Department of Internal Medicine, Intensive Care Unit (ICU) between 10.05.2019 and 01.08.2019. Our study adhered to the principles outlined in the Helsinki Declaration. Written consent was obtained from the patient and relatives.

Main Points

- In our study, the results of nutritional status in sepsis patients, which cause decreased muscle strength, prolonged ventilator dependency, increased healthcare costs and high mortality due to increased protein catabolism, were examined. Although many heterogeneous data in the literature claim that high protein diet can prevent muscle breakdown, our study showed that high protein diet cannot suppress the increase in various inflammatory markers.

Aim of Work

This study investigated whether normal and high dose protein nutrition had a positive effect on inflammation markers and levels in patients with sepsis.

Case Selection

This study was prospectively examined with sepsis patients admitted to the intensive care unit. Volunteer patients who were diagnosed with sepsis according to the definitions determined by the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) Sepsis 3 meeting, whose intensive care stay lasted longer than 24 hours, who were over the age of 18, and whose informed consent form was signed by the patient or their relatives were included in the study. Patients with any known inflammatory disease or active malignancy were excluded from the study.

According to nutritional status, patients were divided into two groups as group 1 (1.3 grams/kg/day) and group 2 (2 grams/kg/day) protein recipients according to the recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN). All selected patients were fed enterally via nasogastric tube. Patients who could be fed orally and received parenteral nutrition support were not included in the study. Patients who could not tolerate feeding via nasogastric tube or could not tolerate receiving targeted protein support during the study and who developed shock were excluded from the study. Fresubin® Original Fibre (Fresenius Kabi İlaç San. ve Tic. Ltd. Şti) was given as the nutritional content for the patients in order to provide the targeted protein content.

APACHE II, SAPS and SOFA score values from intensive care scoring systems showing disease severity in the patient group were used. APACHE II, SAPS and SOFA scores of the patients included in the study were calculated using the parameters analyzed in the first 24 hours after admission to the intensive care unit.

Demographic data of the patients, accompanying disease status, APACHE II, SAPS and SOFA scores calculated for the first 24 hours of hospitalization, leukocyte count, C-reactive protein and procalcitonin values measured on the day of hospitalization were recorded.

Lab Investigations

Blood samples sent to the laboratory for routine test analysis were kept for 30 minutes and then centrifuged at 3500 rpm for 15 minutes. After centrifugation, patient sera were placed in Eppendorf tubes and stored at -80C until the study day for the analysis of tests called nesfatin-1, kallistatin, plasminogen activator inhibitor protein-1, and high mobility group box-1. High mobility group box-1 (HMGB1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels were determined by sandwich-ELISA method.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences software version 24.00 (SPSS Inc., USA) program. Descriptive values were expressed as number (percentage) (n) (%) and mean ± standard deviation. According to the normality assessment of continuous variables made with the Kolmogrov-Smirnov and Shapiro-Wilk tests, the nonparametric test Mann-Whitney U test was used for those not conforming to normal distribution; and the Student t test was used for continuous data conforming to normal distribution. The Friedman test was used to compare continuous variables not conforming to normal distribution in dependent groups. The statistical significance level for all tests performed was accepted as $p<0.05$.

RESULTS

Demographic characteristics of the groups, intensive care scoring systems and statistical significance levels are shown in Table 1. No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics ($p>0.05$).

Serum high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels and significance levels of group 1 patients are shown in Table 2. High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin levels of Group 1 patients measured at hour 0 were determined to be high compared to the levels at hour 24 and hour 48.

Serum leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels and significance levels of Group 1 are shown in Table 3. The zeroth hour leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels of Group 1 patients were determined to be higher compared to the 24th and 48th hour levels.

Serum high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels and significance levels of Group 2 are shown in Table 4. Zeroth hour high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels of Group 2 patients were determined to be high compared to the 24th and 48th hour levels.

Serum leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels and significance levels of Group 2 are shown in Table 5. The zeroth hour leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels of Group 2 patients were determined to be higher compared to the 24th and 48th hour levels.

The comparison of the percentage changes in high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 between the groups at 0, 24 and 48 hours is given in Table 6.

Table 1. Comparison of demographic characteristics of groups

	Group 1 (30)	Group 2 (30)	p
Age*	65,73±13,76	61,40±15,45	0.256
Sex			0.300
Male,n(%)	20(%66,7)	16(%53,3)	
Female, n(%)	10(%33,3)	14(%46,7)	
Body weight kg)	77.5(71/95)	76(71/95)	0.608
Lenght (meter)	1.76(1.63/1.81)	1.76(1.63/1.81)	0.283
BMI (kg/m2)	25(22/34)	25(22/34)	0.316
APACHE II	18(11/43)	22(8/39)	0.343
SAPS	59(4/109)	59(28/80)	0.286
SOFA	10(3/17)	13(2/17)	0.190

APACHE II: APACHE II score, SAPS: SAPS score,

* Mean±standard deviation

Table 2. High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels of group 1 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
HMGB-1	1.71(0.45/12.43)	1.04(0.07/13.58)	0.53(0.16/12.02)	0.001
Kallistatin	22.83(14.28/562.85)	16.88(2.57/522.39)	14.66(8.51/51.39)	<0.001
PAI-1	8.96(4.73/166.09)	7.66(0.63/195.14)	8(2/172)	0.967
Nesfatin-1	5.02(3.26/82.29)	3.67(0.41/81.06)	3.87(0.95/83.26)	<0.001

Table 3. Prealbumin, white blood cell count (WBC), neutrophil count, C-reactive protein (CRP) and procalcitonin (PCT) levels of Group 1 patients at 0, 24 and 48 hours

	Zeroth hour	24th hour	48.th hour	p
Prealbumin	11.20(4.10/30)	10.80(2.90/30.50)	10.70(3.30/28)	0.318
WBC	12660(6130/20640)	12470(5260/22160)	12880(5230/31790)	0.587
Neutrofil	10180(4100/18220)	10090(2640/19760)	11040(1860/24230)	0.670
CRP	90.02(10.4/206.50)	79.62(17.91/185.50)	65.80(15.16/227.80)	0.670
PCT	2.36(0.29/102.40)	1.85(0.22/51.98)	2.80(0.27/125.61)	0.008

Table 4. Nesfatin-1, kallistatin, plasminogen activator inhibitor-1 and high mobility group box-1 levels of group 2 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
HMGB-1	0.60(0.14/0.93)	0.54(0.18/2.25)	0.67(0.16/1.13)	0.644
Kallistatin	15.23(11.08/45.34)	19.13(9.79/41.32)	16.59(6.88/26.01)	0.046
PAI-1	7.91(1.88/9.46)	7.01(1.44/10.11)	7.12(1.93/10.11)	0.670
Nesfatin-1	4.32(0.89/6.31)	4.83(0.86/6.37)	4.47(1.16/6.35)	0.079

Table 5. Leukocyte count (WBC), neutrophil count, C-reactive protein (CRP) and procalcitonin (PCT) levels of Group 2 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
WBC	19860(1890/26650)	19420(4370/38950)	19020(1220/37890)	0.007
Neutrophil	16260(5500/21970)	14840(3850/34660)	15510(3690/33930)	0.061
CRP	191(44.20/297.30)	175.90(35.40/348.70)	159.80(5.47/450)	0.061
PCT	5.30(1.11/81.58)	4.50(1.10/39.48)	3.13(0.81/76.86)	<0.001

Table 6. Comparison of the percentage changes in high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin among the groups at 0, 24 and 48 hours

	Group 1	Group 2	p
HMGB-1 24th hour change (%)	26.56	23.13	0.882
HMGB-1 48.hour change (%)	-55.45	7.60	<0.001
Kallistatin 24.hour change(%)	19.20	27.40	0.001
Kallistatin 48.hour change(%)	-24.33	-2.13	0.008
PAI-1 24.hour change(%)	-7.6	4.40	0.836
PAI-1 48.hour change(%)	-17.13	0.93	0.287
Nesfatin-1 24.hour change(%)	-27.4	6.23	<0.001
Nesfatin-1 48.hour change(%)	-37.77	6.07	<0.001

DISCUSSION

Sepsis is a clinical syndrome of physiological, biological, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. Sepsis and the resulting inflammatory response can lead to multiple organ dysfunction and death. In the late 1970s, it was estimated that there were 164,000 cases of sepsis per year in the United States (US) [3]. Since then, sepsis rates in the US and elsewhere have been increasing steadily, although many are derived from academic institutions or from demand-based analyses [4,5]. Possible reasons for the increased incidence of sepsis include advancing age, immunosuppression, and the emergence of multidrug-resistant microorganisms [6,7]. Although this is not a proven hypothesis, increased awareness through education and awareness campaigns may be effective in early diagnosis of sepsis.

Sepsis is a life-threatening condition associated with a systemic inflammatory response to microbial infection [8]. Sepsis is the most common cause of death in intensive care units, with a fatality rate of 80% due to the development of multiple organ failure. Exaggerated systemic inflammatory mediator synthesis is thought to cause septic shock and death [9].

Despite many therapeutic interventions aimed at controlling the immune system in order to stop the progression to organ failure, the desired success may not be achieved [10]. This simple fact has led to an increase in studies on the pathogenesis of sepsis. In the United States, it causes 150,000 deaths per year, more than the combined deaths of patients with breast, colon, prostate, and brain tumors [11,12].

The onset and progression of systemic inflammation leads to the onset of sepsis and the onset of a hypermetabolic state at the cellular level [13]. Indicators of the septic immune response, such as high fever, increased protein synthesis, tachycardia, and tachypnea, require energy supply above physiological needs. Some sources state that daily energy needs in septic patients can be as high as 10,000 calories [14]. This hypermetabolic state cannot be compensated by high caloric support alone.

The decrease in total body mass during critical illness is a serious intensive care problem seen worldwide. Skeletal muscle proteins are the primary sources for the synthesis of immunoglobulins and acute phase reactants. Muscle protein loss occurs rapidly in critical care patients, and muscle loss associated with a deficiency in total body nitrogen balance of up to 18% can be seen, especially in the first 10 days of intensive care hospitalization. The extent of protein loss may be associated with morbidity and mortality [15,16].

Dietary amino acids must be added to the structure of functional proteins to protect them from oxidation due to their structure. Proteins in the structure of skeletal muscles are the largest protein depot in the body and respond to anabolic nutrition. Amino acids of muscle proteins can be rapidly released and used in stress situations such as starvation and sepsis. If a person does not have enough protein intake to meet daily protein requirements, a negative protein balance develops in the body and skeletal muscle atrophy, impaired muscle growth and a decrease in functional capacity occur. Especially in elderly patients, the decrease in food intake over time increases the risk of complications in geriatric intensive care patients.

Muscle growth depends on protein consumption and hyperaminoacidemia, which stimulates muscle synthesis and, to a lesser extent, reduces muscle protein. When dietary protein consumption is insufficient to meet daily requirements, skeletal muscle atrophy occurs due to negative protein balance. This results in impaired muscle growth and functional decline. It has been reported that the use of dietary amino acids for muscle protein synthesis is more blunted and impaired in healthy older adults compared to young people. Metabolic studies have shown that this anabolic resistance can be overcome with higher levels of protein/amino acid intake [17,18]. Many studies indicate that 25-30 grams/day protein intake is the optimum dose to stimulate maximum quality protein synthesis in adults [19-23]. It is thought that adequate protein supplementation should be the basic approach to preventing protein energy malnutrition and improves clinical outcomes [24,25].

In a study by Singer et al. published in the journal of the European Society of Clinical Nutrition and Metabolism (ESPEN), a daily protein intake of 1.3 grams/kg of protein is recommended during critical illness [26]. However, the same study also states that patients on a high protein diet have positive clinical outcomes. In a study by Weijs et al. including 886 patients, a reduction in 28-day mortality was reported in patients receiving 1.2-1.5 g/kg/day of protein [27]. In a study by Allingstrup et al., a dose-dependent improvement in survival was found in a study by high protein intake [28]. In a retrospective study, Song et al. showed that critically ill patients on mechanical ventilation who achieved 90% of the targeted protein intake had significant improvements in intensive care outcomes [29]. Various studies have suggested that daily protein intake in critically ill patients should be 2.0-2.5 grams/kg/day [30,31]. In this study, patients who were clinically diagnosed with sepsis according to Sepsis 3 criteria, could not be fed orally, and did not receive parenteral nutrition were included in the intensive care unit. The nutritional status of sepsis patients was arranged according to their body weight. They were divided into two groups according to their nutritional status as group 1 (1.3 grams/kg/day) and group 2 (2 grams/kg/day) protein recipients. All selected patients were fed enterally via nasogastric tube. Fresubin® Original Fibre was given as the nutritional content of the patients in order to provide the targeted protein content. The aim of this study was to determine the effects of normal and high-dose protein supplementation on inflammatory and anti-inflammatory proteins in critically ill patients with sepsis. For this purpose, High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin levels were examined.

High mobility group box-1 is a protein found in the nucleus and cytoplasm of almost all cell types. It is actively secreted by immune system cells in response to infection or injury. HMGB-1 is also a potent proinflammatory cytokine and is associated with inflammatory diseases such as sepsis. In our study, serum HMGB-1 levels increased by 26.56% at 24 hours compared to 0 hours in group 1 patients and by 23.13% in group 2 patients ($p=0.882$). However, while there was a 55.45% decrease in serum HMGB-1 levels at 48 hours compared to 0 hours in group 1 patients, a 7.60% increase was detected at 48 hours in group 2 patients. This situation shows that the HMGB-1 molecule, which has a half-life of 17 minutes, is synthesized more in patients fed with high doses of protein than in patients fed with standard doses of protein [32]. Therefore, high-dose protein supplementation in critically ill patients in order to prevent the destruction of muscle proteins may increase the synthesis of inflammatory proteins and increase the risk of inflammation, septic shock and multiple organ failure.

Kallistatin is an endogenous serine protease inhibitor and its serum level decreases in case of inflammation. In the study conducted by Lin WC et al. on 86 intensive care patients, it was determined that the serum kallistatin level was lower in patients with septic shock compared to patients with severe sepsis [33]. In our study, the serum kallistatin level increased by 19.20% at 24 hours compared to 0 hours in group 1 patients and by 27.40% in group 2 patients ($p<0.001$). However, while there was a 24.33% decrease at 48 hours compared to 0 hours in group 1 patients, a 2.13% decrease was detected at 48 hours ($p=0.008$). Although it is an anti-inflammatory molecule, the increase in serum levels in patients fed with high protein may be attributed to exaggerated nonspecific protein synthesis in the first 24 hours when the inflammatory cascade is triggered in sepsis patients with systemic inflammatory response syndrome at the center of their pathogenesis. This also reveals the fact that adequate protein support is necessary for the increase in the synthesis of anti-inflammatory molecules.

Plasminogen activator inhibitor-1 (PAI-1), an important regulator of fibrinolysis, has been identified as a potential biomarker for the diagnosis of sepsis. Plasminogen activator inhibitor-1 (PAI-1) inhibits plasminogen activator, a key enzyme involved in the cleavage of plasminogen into plasma. In a study of 363 patients by Tiope et al., it was found that PAI-1 levels were higher in

patients with severe sepsis compared to patients with sepsis [34]. In our study, serum plasminogen activator inhibitor-1 levels decreased by 7.60% at 24 hours compared to 0 hours in group 1 patients, while they increased by 4.40% in group 2 patients. However, in group 1 patients, there was a 17.13% decrease at 48 hours compared to 0 hours, while there was a 0.93% increase at 48 hours. The increase in PAI-1 levels, which is a part of the inflammatory process in sepsis patients fed with high doses of protein, has been interpreted as high protein replacement may trigger the inflammatory process.

Nesfatin-1 is a peptide secreted by peripheral tissues, central and peripheral nervous system. Nesfatin-1, which is related to food intake and water consumption, is related to energy homeostasis. Nesfatin-1 can cross the blood-brain barrier bidirectionally. In a study conducted by Özsavcı et al. on rats, it was revealed that the nesfatin-1 molecule has an anti-inflammatory effect [35]. However, in another study conducted with patients with chronic obstructive pulmonary disease, it was claimed that the nesfatin-1 molecule may have inflammatory effects [35]. In our study, serum nesfatin-1 level decreased by 27.40% in group 1 patients at 24 hours compared to hour 0 and increased by 6.23% in group 2 patients. However, while there was a 37.77% decrease in group 1 patients at hour 48 compared to hour 0, an increase of 6.07% was detected in group 2 patients at hour 48. The nesfatin-1 molecule may have different effects on inflammatory mechanisms in the central nervous system and the peripheral nervous system. The increase in serum nesfatin-1 levels in sepsis patients fed with high doses of protein has been interpreted as high protein replacement may trigger the inflammatory process.

CONCLUSION

Preservation of muscle mass and prevention of muscle protein breakdown in critical care patients is an important goal in reducing the duration of intensive care, the need for mechanical ventilation support, and the risk of complications. This need should be managed more carefully in diseases where the catabolic process is more intense, such as sepsis. Protein supplementation at a dose of at least 1.3 g/kg/day is recommended for critical care patients in order to prevent muscle breakdown. In our study, it was determined that the synthesis of many inflammatory molecules increased at 48 hours in the patient group receiving high-dose (2 g/kg/day) protein supplementation. There are not yet sufficient studies in the literature investigating the effect of high protein supplementation on the inflammatory process in critically ill patients. Prospective and randomized controlled studies with a larger number of patients are needed to support our study data.

Conflict of interest: None declared.

Informed Consent: Received.
Informed Consent: Written permission was obtained from the patients

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Ethical Approval: The Gaziantep University Clinical Researches Ethics Committee authorized the research design (Approval date: 08.05.2019).

Author Contributions: Conception: YH; TG - Design: TG- Supervision: YH - Fundings: YH; TH -Materials: YH - Data Collection and/or Processing: YH; TG - Analysis and/or Interpretation: YH - Literature: YH; TG- Review: YH- Writing: YH;TG- Critical Review: YH.

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Original Research

The Efficiency of Different Supplementary Irrigation Techniques After Nickel-Titanium Rotary System in Endodontic Retreatment

Selin Göker Kamalı[1,*], Dilek Türkaydın[1]

[1] Department of Endodontics, Marmara University, Faculty of Dentistry, Istanbul, Türkiye

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Corresponding Author
Selin Göker Kamalı, MD
Address: Marmara University, Faculty of Dentistry, Department of Endodontics, Istanbul, Turkiye
E-mail: dtselingoker@gmail.com

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ABSTRACT

Objective: To assess the efficiency of XP-Endo Finisher file (XPFF), EDDY, and diode laser as supplementary irrigation activation techniques following nickel-titanium rotary files in the endodontic retreatment.

Methods: 48 mandibular premolars were collected. Each root canal was shaped and filled with EndoSequence BC sealer and gutta percha. After 14 days, endodontic retreatment was performed using D-Race instruments. Then, 48 samples were assigned into 4 groups (n=12) as control, diode laser, EDDY, and XPFF according to the supplementary irrigation methods. After the irrigation procedure, all samples were visualized under a stereomicroscope. The remaining root filling material was scored and compared statistically using Kruskal-Wallis and Post-hoc pairwise comparison tests.

Results: In all thirds, there was a significant difference between the diode laser and control groups. The amount of remaining filling material in the diode laser group was significantly lower than in the control group. When the other groups were compared, a significant difference was observed only between the diode laser and XPFF groups in the coronal third.

Conclusion: No supplemental method could eliminate the root obturation material. The diode laser can be used in addition to nickel-titanium rotary retreatment systems to improve the removal of gutta percha and bioceramic sealer.

Keywords: diode laser, EDDY, endodontic retreatment, EndoSequence BC sealer, XP-Endo Finisher.

INTRODUCTION

Endodontic retreatment is the initial option for eradicating bacteria in the root canal if endodontic therapy does not succeed [1]. For optimal disinfection during endodontic retreatment, it is crucial to remove all obturation materials from the canal walls [2]. However, retreatment techniques and instruments cannot completely remove them [3]. Therefore, additional methods or devices have been suggested to improve root canal cleaning during endodontic retreatment [4, 5]. Activation of irrigation solution has been proven to aid in removing remaining root filling materials [6, 7].

Various devices have been produced for irrigation activation. The XP-Endo Finisher file (XPFF; FKG Dentaire SA, La Chaux-

de-Fonds, Switzerland) has a small core and shape memory. At body temperature, these properties enable this instrument to transform into a spoon shape. XPFF may thus induce turbulence in irrigation solutions while also touching the canal walls [8]. The tips of EDDY (VDW, Munich, Germany), a sonic activation method, are made of polyamide and operated with an air scaler. The vibration produced by the air scaler is transferred to the tips in a high-amplitude oscillating motion. According to the manufacturer, this movement generates cavitation and sonic flow, resulting in highly effective cleaning efficiency [9]. Diode laser for irrigation activation has been shown to enhance disinfection and sealing of the root canal system [10, 11]. A recent research proposed the use of diode laser as an adjunct to nickel-titanium (NiTi) retreatment rotary systems to improve the removal of bioceramic sealer [12].

The objective of the current investigation was to assess the efficiency of XPFF, EDDY, and diode laser as supplementary irrigation activation methods in the removal of root canal filling materials. The null hypothesis was that there was no significant difference between the remaining root filling materials after using XPFF, EDDY, diode laser, and conventional needle irrigation.

MATERIALS AND METHODS

G*Power program showed that the sample size should be 12 for each group (α=0.05, power=0.80). Following ethics committee permission (24.03.2022 and 2022/53), 48 straight and single-canal mandibular premolars were selected from the extracted tooth pool. During the selection process, the teeth were meticulously examined, and those with root fillings, immature apices, or root fractures were excluded. A specimen length of 16 mm was achieved by the decoronation process. All treatments were completed by a single endodontist with 10 years of experience.

Main Points

- This study compared the effectiveness of XPFF, EDDY, diode laser and needle irrigation following the D-Race retreatment system for removing bioceramic sealer.
- No supplemental method has been able to completely remove root obturation material.
- Diode laser irrigation after D-Race retreatment files helped to remove bioceramic sealar more efficiently.
- The effects of XPFF and EDDY on the removal of bioceramic sealer and gutta percha were similar to needle irrigation.

Endodontic Treatment

The working length (WL) was established to be 1 mm behind the root apex. Each canal was shaped to size 35/.04 with HyFlex CM (Coltene, Altstatten, Switzerland) files using an endodontic motor (500 rpm/2.5 Ncm). After each rotary instrument, the canals were rinsed with 5.25% NaOCl (Cerkamed, Stalowa Wola, Poland) using a 30-gauge (30G) side-vented needle (Endo-Top, Cerkamed, Stalowa Wola, Poland). Final irrigation was applied with distilled water. Then, each canal was filled with EndoSequence BC sealer (Brasseler, Savannah, GA, USA) and gutta percha using the lateral condensation method. After periapical radiography was taken to validate the perfection of canal obturation, Coltosol (Coltene, Altstatten, Switzerland) was placed in the canal entrances. The roots were kept in an incubator with 37°C and 100% humidity for 14 days.

Root Canal Retreatment

D-Race rotary system (FKG Dentaire SA, La Chaux-de-Fonds, Switzerland) was used for retreatment procedures. The DR1 instruments (15mm, 30/.10; 1000 rpm/1.5 Ncm) were operated to remove the filling material in the coronal third of the root canal. DR2 files (25 mm, 25/.04; 600 rpm/1.5 Ncm) were used in the remaining part of the canal. All retreatment files were operated with brushing movements. After each rotary instrument, the canals were rinsed with 5.25% NaOCl using a 30G side-vented needle. Retreatment was deemed finished when the DR2 file surface showed no signs of gutta percha.

Then, the samples were classified according to the amount of remaining filling material by radiographic examination and were randomly assigned into 4 groups (n=12) accordingly. One of the groups was determined as the control group. In the remaining groups, XPFF, EDDY, and diode laser were used as supplementary irrigation techniques.

Control Group

The canals were irrigated with 5 mL of 5.25% NaOCl for 60 s using a 30G side-vented needle. The needle was placed 1 mm shorter than WL and moved up and down.

Supplementary Techniques

XP-Endo Finisher: The canals were filled with 5.25% NaOCl

using a needle. The irrigant was activated by the XPFF on the endodontic motor (800 rpm/1 Ncm). The plastic rubber stop was set 2 mm behind the WL and XPFF was operated with an up-and-down motion for 20 s. In 3 cycles, each canal was rinsed with 5 mL of NaOCl in total.

EDDY: The canals were filled with 5.25% NaOCl using a needle. The irrigant was activated by the EDDY tip on the air scaler. The EDDY tip was inserted 2 mm behind the WL and operated with an up-and-down motion for 20 s. In 3 cycles, each canal was rinsed with 5 mL of NaOCl in total.

Diode Laser: The canals were filled with 5.25% NaOCl using a needle. The irrigant was activated with an 810 nm diode laser (Cheese™, Gigaa, China). The optical fiber tip (200 µm) was placed 2 mm shorter than WL and moved helically from apical to coronal (1.5 W, continuous mode). The activation was carried out 4 times, each time for 7 s, with 10 second-interval between irradiations. At these intervals, each canal was rinsed with 5 mL of NaOCl in total.

In all groups, the final flush was performed with 5 mL of 17% EDTA (Cerkamed, Stalowa Wola, Poland) followed by 5 mL of distilled water using a needle.

Analysis of Remaining Filling Material

With diamond discs (Meisinger, Neuss, Germany), grooves were created on the buccal and lingual surfaces of the samples, which were not deep enough to extend into the canal. The roots were longitudinally split by placing the chisel in the grooves.

The samples were visualized under a stereomicroscope (Leica Microsystems, Wetzlar, Germany) at 20X magnification. The grading system of Ezzie et al. [13] was used to score the remaining filling material on the canal walls (Figure 1):

1 = No to slight presence (0-25%) of filling material,
2 = Some presence (25-50%) of filling material,
3 = Moderate presence (50-75%) of filling material,
4 = Heavy presence (>75%) of filling material.

The remaining obturation material in the coronal, middle, and apical third of each canal was scored by two blinded endodontists. The observers re-evaluated the images after 1 month. Observer reliability was determined using the kappa test. The intraobserver and interobserver agreement values were 0.824, 0.897, and 0.846, respectively.

Figure 1. Stereomicroscope images of representative samples. a) The apical third of the root canal was graded as score 4, and the coronal and middle thirds as score 1. b) The coronal third of the root canal was graded as score 2, and the middle and apical thirds as score 3.

Statistical Analysis

The data distribution was analyzed using the Shapiro-Wilk test. The remaining obturation material in the groups was compared using the Kruskal-Wallis and Post-hoc pairwise comparison tests. The significance level was accepted as 0.05.

RESULTS

Obturation material was detected in every root canal. The mean and standard deviation (SD) scores of the remaining root filling material for all thirds are shown in Table 1. The amount of remaining filling material in the diode laser group was significantly lower than in the control group for all thirds. When the other groups were compared, a significant difference was observed only between the diode laser and XPFF groups in the coronal third (Table 2).

Table 1. Mean and standard deviation (SD) scores of the remaining root filling material for all thirds

	Groups	n	Mean	Median	SD	Minimum	Maximum	p
Coronal	Control	12	2.17	2.00	1.115	1	4	**0.005**
	EDDY	12	1.17	1.00	0.577	1	3	
	XPFF	12	1.58	1.00	0.996	1	4	
	Diode laser	12	1.08	1.00	0.289	1	2	
Middle	Control	12	2.50	2.50	1.314	1	4	**0.049**
	EDDY	12	1.58	1.00	0.996	1	4	
	XPFF	12	1.75	1.00	1.055	1	4	
	Diode laser	12	1.25	1.00	0.622	1	3	
Apical	Control	12	3.50	3.50	0.522	3	4	**0.013**
	EDDY	12	2.92	3.00	1.165	1	4	
	XPFF	12	3.17	3.50	1.115	1	4	
	Diode laser	12	1.83	1.00	1.193	1	4	

Kruskal-Wallis test, Bold letters indicate significant difference ($p<0.05$).

Table 2. Pairwise Comparison

	Coronal	Middle	Apical
Groups	**p**	**p**	**p**
Control-EDDY	0.409	0.271	0.673
Control-XPFF	0.440	0.455	0.980
Control-Diode laser	**0.017**	**0.047**	**0.011**
EDDY-XPFF	0.484	0.973	0.945
EDDY-Diode laser	1.000	0.778	0.159
XPFF-Diode laser	**0.032**	0.519	0.083

Bold letters indicate significant difference ($p<0.05$).

DISCUSSION

During endodontic retreatment, the existing root canal filling material must be entirely removed to eliminate the microorganisms in the root canal system that cause periapical inflammation. Previous research has shown that D-Race retreatment files cannot completely remove obturation materials from the root canal [14]. Therefore, in the current research, XPFF, EDDY, and diode laser were used following D-Race retreatment files to remove bioceramic sealer and compared with needle irrigation. According to the results, the null hypothesis was rejected since there was a significant difference between the groups. Our findings revealed that compared to needle irrigation, diode laser-activated irrigation improved bioceramic sealer removal, while the XPFF and EDDY did not exhibit any significant difference.

Various approaches, such as radiographic evaluation [15], root splitting [16-18], and micro-computed tomography (micro-CT) [4, 6, 7], have been used to determine the effect of supplementary techniques applied following NiTi retreatment files on the obturation material removal. In the current research, the samples were sectioned longitudinally and the residual obturation material was scored using stereomicroscope images. This technique is more beneficial and trustworthy than radiographic

assessment, which produces only a two-dimensional image. To minimize subjectivity in the scale-based scoring method, images were evaluated by 2 blinded endodontists, and interobserver and intraobserver agreement values were calculated. Micro-CT yields more accurate results since it visualizes the root canal in three dimensions without damaging the sample. Nevertheless, access to this technology is limited due to high cost.

The findings of the present research revealed that diode laser removed more obturation material than conventional needle irrigation. This is consistent with a recent study using micro-CT analysis [12]. Furthermore, a previous study using SEM analysis reported that combining Er,Cr:YSGG with a diode laser largely eliminated resin sealer residues from the canal walls [19]. Cheng & Zhu [18] concluded that Nd:YAG laser could help to remove the resin-based sealer. Photon-initiated photoacoustic streaming (PIPS) irrigation has also been shown to improve the removal of tricalcium silicate-based sealer [20]. However, Dönmez Özkan et al. [21] observed that PIPS was not effective in removing resin-based sealer as a supplementary technique.

Earlier investigations have demonstrated that supplementary irrigation with the XPFF during endodontic retreatment improves the removal of filling material regardless of sealer type [6, 22]. Conversely, we discovered no significant difference between XPFF and needle irrigation. This disparity might be related to the use of different analysis techniques for the residual obturation material. While the root splitting and scoring method were used in this research, the residual filling material was analyzed with micro-CT in the previous studies [6, 22]. The most recently published study assessing the removal of EndoSeal MTA from artificial grooves on the canal wall found no significant difference between XPFF and needle, similar to our findings. However, they discovered a significant difference between the EDDY and needle, which contradicts our results [23]. The reason for this contradiction may be that they used only root canal sealer as obturation material. In the present study, EDDY may not have effectively eliminated gutta percha.

Bioceramic materials have become increasingly preferred as root canal sealers because of their biocompatibility and antibacterial effects [24]. Bioceramic sealers chemically bond to dental structures [25, 26], which can make them difficult to retreat. The absence of difference between the EDDY, XPFF, and diode laser groups in this research might be attributed to the difficulty of removing EndoSequence BC sealer. However, only Oltra et al. [27] stated that AH Plus sealer can be removed more effectively than EndoSequence BC sealer. While some research revealed similar retreatability [6, 28, 29], another study demonstrated less sealer residue with EndoSequence BC sealer compared to AH Plus [30].

On the other hand, no previous investigation has compared the effectiveness of EDDY and XPFF with diode lasers in the removal of root obturation material. The possibility of damage to the dentin and obturation material during root splitting process was a limitation of the current study. To obtain more precise results, future studies should compare the efficacy of diode lasers with EDDY and XPFF using micro-CT. Another limitation of the research was the removal of tooth crowns to ensure an equal WL. Although decoronation is not reflective of clinical practice, it does minimize factors such as crown anatomy and access cavity. As a result, more reliable data on the instruments' effectiveness is collected.

CONCLUSIONS

Under the experimental conditions of this investigation, no supplemental irrigation method might completely remove the obturation materials. The diode laser can be used in addition to NiTi rotary retreatment systems to improve the removal of gutta percha and bioceramic sealer.

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Conflict of interests: The authors deny any conflicts of interest related to this study.

Ethical Approval: This study was approved by the Marmara University Faculty of Dentistry Ethics Committee (24.03.2022 and 2022/53).

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Original Research

The Importance of Diagnostic Mediastinoscopy in Patients with Mediastinal Lymphadenopathy

Rüçhan Anbar[1,*], Abidin Şehitoğulları[2]

[1] Departmant of Thoracic Surgery, Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital, İstanbul, Türkiye
[2] Departmant of Thoracic Surgery, Faculty of Medicine, Sakarya University, Sakarya, Türkiye

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Corresponding Author
Rüçhan Anbar, MD
Addresss: Sancaktepe İlhan Varank Training ans Research Hospital, Emek, Namık Kemal Cd. No:54, 34785 Sancaktepe, İstanbul, Türkiye
E-mail: ruchananbar@hotmail.com

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ABSTRACT

Objectives: Mediastinoscopy is a safe and invasive diagnostic method allowing to obtain sufficient tissue samples in the diagnosis of many malignant and benign intrathoracic diseases. In this study, it was aimed to determine the importance of mediastinoscopy in diagnosing mediastinal diseases and also provide patient data in the resolution of mediastinal diseases.

Methods: Between January 2016 and December 2020, 76 cases of mediastinal lymphadenopathy that could not be diagnosed by other diagnostic methods were evaluated.

Results: 64 (84,2%) of these 76 cases were diagnosed by mediastinoscopy. 12 cases (15.7%) were reported as reactive lymphoid hyperplasia. Since the definitive diagnosis of these cases could not be proven, they were considered as false-negative. Histopathological examination revealed chronic granulomatous lymphadenitis in 16 cases, non-necrotizing granulomatous lymphadenitis in 27 cases, metastasis of malignant disease in 18 cases, and lymphoma in 2 cases. In our study, the sensitivity of mediastinoscopy was determined as 84.2%. Neither mortality nor morbidity was detected in our cases.

Conclusion: As a result, mediastinoscopy continues to maintain its traditional place for patients that cannot be diagnosed, because it is reliable and less invasive.

Keywords: granulomatous lymphadenitis, lymphoid hyperplasia, mediastinoscopy

INTRODUCTION

Mediastinoscopy is an important method in diagnosing and planning the treatment of diseases such as mediastinal lymphadenopathy, carcinoma metastases, sarcoidosis, tuberculosis, lymphoma and mediastinal tumors. Mediastinal lymph node evaluation was initiated by Albert C. Daniels in 1949. Further developed by Carlens (1959) and Pearson (1965), by making a suprasternal incision, mediastinoscopy has become a popular surgical method for diagnosing and staging purposes [1, 2]. As indicated in the studies, in cases that cannot be diagnosed with other methods, it is a safe and effective diagnostic method in which sufficient tissue samples can be obtained. Lymph node

examination maintains its importance with its short hospital stay, 1-2% morbidity and low mortality [3].

According to the mediastinal lymph node map, developed by Mountain and Dressler, mediastinal lymph node stations are as follows: 2R, 2L, 4R, 4L and station number 7. It is advised to proceed a biopsy considering the mentioned stations [4]. Endoscopic ultrasonography (EUS) and endobronchial ultrasound (EBUS), which have recently been used in the evaluation of mediastinal lymphadenopathies, have also become popular tool methods nowadays. Although the specificities of these techniques were found to be high, their negative predictive values were low. Preoperative mediastinoscopy has a sensitivity of more than 90% and a specificity of 100% in lung cancer staging. Considering these values, it is reasonable to state that mediastinoscopy is a reliable method that is widely used. Mediastinoscopy maintains its traditional place for patients that cannot be diagnosed [4-6].

In this study, the place and importance of diagnostic mediastinoscopy were evaluated.

MATERIALS AND METHODS

Between January 2017 and December 2020, 76 patients (32 males and 44 females) with mediastinal lymphadenopathy that could not be diagnosed with other diagnostic methods were evaluated by videomediastinoscopy in the Department of Thoracic Surgery of Sakarya University Training and Research Hospital. Mediastinoscopies for staging were not included in the study. All surgical procedures were performed under general anesthesia in operating room conditions. Sampling was done from peritracheal, paratracheal and subcarinal (2R, 2L, 4R, 4L, 7) stations in the mediastinal lymph node map.

RESULTS

A total of 76 patients who mediastinal lymphadenopathy were included in the study. Amongst all the patients, 42% (n=32) were males and 58% (n=44) were females. Mean age was 44.9 ± 8.2 years ranging from 24 to 77 years. Diagnosis was made by mediastinoscopy in 64 (84.2%) of 76 cases that could not be diagnosed by other noninvasive and invasive diagnostic methods. The remaining 12 cases (15.7%) were reported as reactive hyperplasia. Since the definitive diagnosis of these cases could not be proven, they were considered false-negative. Histopathological examination revealed chronic granulomatous lymphadenitis in 16 cases, non-necrotizing granulomatous lymphadenitis in 27 cases, metastasis of malignant disease in 18 cases, and lymphoma in 2 cases (Table 1).

With these findings, the sensitivity was evaluated as 84.2%. No mortality or morbidity was found in the cases.

Table 1. Histopathological diagnosis

Histopathological diagnosis	Number of cases (Rate %)
Non-necrotizing granulomatous lymphadenitis	27 (% 35.5%)
Chronic granulomatous lymphadenitis	16 (21%)
Reactive lymphadenitis	12 (15.7%)
Lung adenocarcinoma metastasis	6 (7.8%)
Small cell lung cancer metastasis	4 (4.7%)
Squamous cell lung cancer metastasis	3 (3.9%)
Lymphoma	2 (2.6%)
Anthracosis	2 (2.6%)
Calcified lymph node	1 (1.3%)
Thymoma	1 (1.3%)
Sarcoma	1 (1.3%)
Stomach cancer	1 (1.3%)

DISCUSSION

Mediastinoscopy has an indispensable role in the diagnosis of unidentified cases (such as sarcoidosis, tuberculous lymphadenopathy, tumor metastases, lymphomas) having mediastinal lymphadenopathy. Studies have shown that the sensitivity of cervical mediastinoscopy varies between 72% and 89% (mean 81%) [7, 8]. In the study of Gunda Leschber et al., the sensitivity was found to be 93.7% [9]. In this study, a diagnostic success rate of 84.2% was achieved. The findings were compatible with the literature data.

Depending on the underlying disease, epithelioid granulomas resembling sarcoidosis can be seen in regional lymph nodes for many reasons [10, 11]. In the study of Kaya et al. [12] the most common cause was sarcoidosis (82, 61.2%) and tuberculosis (24, 17.9%) was the second most common cause in 134 patients with granulomatous lymphadenitis. In another study conducted in Turkey, 124 (85.5%) of 145 cases that could not be diagnosed by other methods were diagnosed by mediastinoscopy, and chronic granulomatous lymphadenitis was found in 64 cases (44.1%) and non-necrotizing granulomatous lymphadenitis was found

in 25 cases (17.2%) [13]. In parallel with these data, we see that granulomatous diseases constitute the majority of diagnoses in our study. We found the rate of non-necrotizing lymphadenitis (27/76) to be 35.5%, and the rate of necrotizing lymphadenitis (16/76) to be 21%. Granulomatous lymphadenitis accounts for 56.5% of our cases.

The most common cause of malignant mediastinal lymphadenopathy is metastatic lung cancer. Other causes of malignant mediastinal lymphadenopathy can be listed as lymphomas [14]. Lung cancer is the most frequently diagnosed cancer in both gender and remains the leading cause of cancer deaths. The 5-year survival rate in lung cancer is only 18% due to late diagnosis. Also, about 40% of cancer deaths are due to lung cancer. However, considering that more than half of the patients in lung cancer are diagnosed at an advanced stage, diagnosis and staging of lung cancer are very important [15, 16]. Identification and confirmation of pathology is critical for early diagnosis and improving survival. In clinical practice, fiberoptic bronchoscopy, CT-guided PTNB (Percutaneous Transthoracic Needle Biopsy), ENB (Electromagnetic Navigation Bronchoscopy), EBUS-TBNA (Endobronchial Ultrasonography-Transbronchial Needle Aspiration) and mediastinoscopy are the methods used for diagnosis [16, 17].

EBUS-TBNA is suitable for lesion biopsy in the subcarinal and bilateral hilar regions. Mediastinoscopy is required for larger tissue sampling in suspicious cases, especially in cases where no diagnosis can be made because of relatively high false-negative rates at stations 4R or 7. EBUS-TBNA is relatively safe, but mediastinoscopy provides more tissue uptake and better diagnostic yield for lymph nodes 4R and 7 [17]. If EBUS-TBIAB and EUS-IAB are used together, it has been observed that the sensitivity is increased in mediastinal staging, especially in lung cancers. When EBUS is combined with EUS, paraoesophageal (station 8), pulmonary ligament (station 9) lymph nodes in the lower zone can be evaluated. In a study by Wallace et al., the sensitivity was found to be 69%- and 93% in malignant mediastinal lymph nodes when only EBUS and EBUS-TBIAB+EUS-IAB were performed together, respectively [15]. Further, mediastinoscopy is a valuable method with its high sensitivity rate and larger tissue sampling in the diagnosis of mediastinal lung cancer and other cancer metastases that cannot be detected by other diagnostic methods. The morbidity rate is 1-2% and the mortality rate is 0.3-0.08% [3, 15, 17]. No morbidity or mortality was found in our study.

CONCLUSIONS

Mediastinoscopy sustains its traditional place in cases that could not be definitively diagnosed and requiring tissue diagnosis that cannot be accomplished with less invasive methods. Mediastinoscopy is a safe, fast and effective method for diagnosis and treatment of mediastinal lymph nodes, which are frequently affected by cancer metastases and granulomatous diseases.

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

Informed Consent: Informed consent document was obtained from the study participants.

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Conception: - Design: Rüçhan Anbar
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Data Collection and/or Processing: Rüçhan Anbar
Analysis and/or Interpretation: Rüçhan Anbar
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Review: Rüçhan Anbar, Abidin Şehitoğulları
Writing: Rüçhan Anbar
Critical Review: Rüçhan Anbar, Abidin Şehitoğulları

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Original Research

Therapeutic Effect of Thymoquinone on Melatonin, Ferritin, and Renal Function in Renal Ischemia/Reperfusion Injury in Rats

Ahmet Sarper Bozkurt[1, *], Şenay Görücü Yılmaz[2]

[1] Department of Physiology, University of Gaziantep, Faculty of Medicine, Gaziantep, Türkiye
[2] Department of Nutrition and Dietetics, University of Gaziantep, Faculty of Health Science, Gaziantep, Türkiye

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Corresponding Author
Ahmet Sarper Bozkurt, PhD
Address: Department of Physiology Gaziantep University, Medicine Faculty, Gaziantep, Türkiye
E-mail: asbozkurt@gantep.edu.tr

ABSTRACT

Objective: Ischemia/reperfusion (I/R) injury is the period of tissue or organ damage that develops after the tissue's blood flow is restored. The extent of damage varies according to the severity of tissue and cell damage. Thymoquinone (TQ) has a wide therapeutic spectrum. The effect of thymoquinone on melatonin and ferritin in I/R can regulate renal function by combining these two mechanisms to improve damage. Therefore, the effect of thymoquinone on melatonin and ferritin levels in renal I/R as well as its regulatory role in renal functions have been investigated.

Methods: Thirty-six male *Sprague Dawley* rats were included in the study (250-300 g, 8-10 weeks). The rats were randomly assigned to 6 groups with 6 animals in each group. Groups; 1- Control, 2- Sham, 3- Solvent, 4- Renal ischemia/reperfusion injury (I/R), 5- I/R+ Thymoquinone (TQ) (5 mg/kg/day), 6- TQ (5 mg/kg/day). The dorsal region of the rats was surgically opened, and the left renal artery was clamped for 30 minutes and then reperfused for 24 hours. TQ (i.p) was applied to the treatment groups for 15 days. At the end of the experiment, blood samples were taken from all groups, and kidney function tests (Na^+, K^+, Creatinine, urea, BUN) were performed. Melatonin and ferritin levels were analyzed by the ELISA method from kidney tissue samples.

Results: Data showed that short-term TQ treatment was effective on serum K^+ ($P = 0.010$) and melatonin and ferritin levels in kidney tissue. Melatonin and iron activity, which were normal in healthy groups, melatonin decreased and ferritin increased significantly in the I/R group. TQ treatment positively regulated the dysregulation of these two molecules in I/R.

Conclusion: TQ may contribute to the healing of the damage by improving the K^+ levels, which indicates the insufficiency of kidney functions in I/R damage. Melatonin and ferritin, as interacting molecules in I/R, are regulated by TQ, indicating that they may contribute to the management of I/R damage.

Keywords: Ischemia/reperfusion injury, melatonin, ferritin, thymoquinone.

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INTRODUCTION

Ischemia/reperfusion (I/R) injury is the damage that occurs after the blood flow to a specific organ or tissue is interrupted and blood flow is restored [1]. I/R can occur in many organs or tissues. I/R seen in renal tissue is the major cause of acute kidney injury. A sudden and temporary decrease in kidney function results in inflammation, oxidative stress, fluid, and electrolyte dysregulation [2]. Even if the tissue is reperfused, the damage may be permanent. Thymoquinone (TQ) is a compound with a rich therapeutic potential in many aspects. The compound contained in *Nigella sativa* has given positive results in similar injuries such as ovarian injury [3], renal transplantation [4], spinal cord [5], and intestinal I/R [6]. Although melatonin treatment is applied in renal I/R, the effect of TQ application on melatonin and ferritin levels is not clear. Melatonin is a powerful antioxidant. Meta-analyses indicate the therapeutic and protective properties of melatonin [7]. Additionally, melatonin treatment is suggested to have prophylactic and therapeutic effects against acute kidney injury in I/R patients with obesity. Studies mostly show its preventive effect. In the treatment of the damage with TQ, an improvement that can occur through melatonin and ferritin can provide the regulation of many renal functions together. Ferroptosis is an iron-dependent cell death mechanism and a source of cellular iron load. Ferroptosis is an important mechanism in cerebral I/R [8]. Ferritin is also the largest source of cellular oxidative stress. The increase in oxidative load after I/R contributes to kidney damage. Cellular iron overload is among the causes of many diseases. Iron chelators are one of the treatments used to reduce iron overload. Side effects of chelators and patient compliance are disadvantages. Studies have shown that melatonin can chelate iron and scavenge free radicals. At the same time, melatonin's inhibition of lipid peroxidation indicates its effective role in the ferritin process [9]. Function tests in renal I/R provide information about the kidney's working discipline. These tests, which play an important role in diagnosis and treatment, also provide important data in drug trials [10]. Studies have found that urea and creatinine levels increase and electrolyte values deteriorate in renal I/R [11]. In this study, we investigated the effects of TQ on melatonin and ferritin renal functions in the I/R rat model. In addition to its many properties, TQ is likely to have the functionality of repairing damage via melatonin and ferritin.

Main Points

- This study suggests that TQ may affect melatonin and ferritin molecules separately or may play a role in compensating for I/R injury by acting in a melatonin-ferritin or ferritin-melatonin direction.
- This study is the first to evaluate the relationship between melatonin and ferritin with renal function tests in rats with a renal ischemia model.

MATERIAL AND METHODS

Ethical standards and laboratory condition

Ethical permissions for the study were obtained from the Gaziantep University Experimental Animals local ethics committee (decision number:2024/49, protocol number:398). Thirty-six adult male Sprague Dawley rats (250-300 g, 8-10 weeks) were included in the study. The rats were randomly assigned to 6 groups with 6 rats in each group. The rats were housed individually in standard cages at 22-24 °C under a 12h dark/12h light cycle until the end of the study. The rats had ad libitum access to water and food. Injections and sampling were performed at 9-11 am.

Experimental groups and treatments

Rats were anesthetized with 75 mg/kg (Ketalar, 002038, Eczacıbaşı Health Products Industry and Trade Inc., Lüleburgaz, Turkey) ketamine and 10 mg/kg (Alfazyne, 0804125-11, Alfasan, Woerden, Holland) xylazine intraperitoneally before the surgical procedure. The rats were shaved with a shaver on the left renal area under anesthesia and the skin, fascia, and muscle layer were cut 1.5 cm vertically-laterally with surgical scissors. The kidney was removed and the renal artery was clamped. The kidney was observed for a few minutes to change color for ischemia and was reperfused for 24 hours after waiting for 30 minutes. Finally, TQ was applied.

Experimental groups

Control group (n= 6); Ad-libitum feeding without any intervention. No surgical procedure was performed.

Sham group (n=6); The back regions were opened and closed without any procedure.

Solvent group (n = 6); 2 ml i.p applied for 15 days (Ethanol: PBS (pH 7.2) (1:1) (Cayman, 15039). No surgical procedure was performed.

Ischemia/Reperfusion injury (I/R); After the back region of the rats was opened, clamping was performed on the left renal artery for 30 minutes. Immediately after the 30 minutes, reperfusion was performed for 24 hours [12].

Ischemia/reperfusion injury (IR) + Thymoquinone (TQ) group (IR+TQ) (n=6); After the rats' back region was opened as surgical, the left renal artery was clamped for 30 minutes. Immediately after the 30 minutes, reperfusion was performed for 24 hours [12]. The incision was closed with a surgical suture and after post-operative care, TQ was dissolved according to the manufacturer's recommendation (Cayman, 15039, USA). Rats were treated with 5 mg/kg/day TQ (i.p) for 15 days [13].

Thymoquinone (TQ) group (n=6); TQ was administered (i.p) for 15 days at 5 mg/kg/day [13].

Renal function tests

Following TQ treatment, 6 ml intracardiac blood samples were taken from rats under anesthesia into gel tubes, and renal function tests were performed from the serum samples obtained Levels of serum urea, BUN, creatinine, Na^+, and K^+ activity were determined by enzymatic-kinetic method in Beckman Coulter AU5400 (Gaziantep University, Sahinbey Research and Practice Hospital Biochemistry Laboratory).

Melatonin and Ferritin Analysis

The clamped left kidney tissue was removed and used for melatonin (Fine Test, ER116) and ferritin (Fine Test, ER0947) analyses by ELISA method. According to the commercial kit protocol for melatonin and ferritin analysis, tissues were immediately dissected on ice (tissue: PBS (1:9)) and homogenized in cold PBS in a homogenizer (IKA) (IKA T25 digital ultra turrax, Germany) at 12.000 rpm for 1 min. Samples were centrifuged at 5000xg for 5 min and the supernatant was analyzed spectrophotometrically by ELISA method. To determine the optical density (OD), 2 replicate measurements were performed at a wavelength of 450 nm. Data were calculated according to a standard curve.

Statistical Analysis

To detect a difference of 0.50 between groups based on historical data, the required minimum sample size was calculated as 6 animals in each group under the conditions of 5% Type I error and 80% power (Type II error 0.20). Power analysis was performed using the MedCalc v.11.3.5 package program. In the statistical evaluation of the data, categorical data were summarized as frequency and percentage, and continuous data were summarized as mean ± standard deviation. Data were presented as the mean ± SD/SEM of at least three independent measurements. Statistical significance was accepted as $P < 0.05$. One-way ANOVA was used for comparisons. Correlations were tested with Pearson. Data were normalized using the Shapiro-Wilk test. Post-hoc analyses were performed using the Tukey test. Statistical significance was accepted as $P < 0.05$.

RESULTS

TQ Improved Renal Function in Renal I/R

K^+ levels measured in serum samples decreased in the I/R+TQ group compared to the I/R group ($P<0.05$) (Figure 1E). TQ treatment may have a regulatory effect on K^+ levels in renal functions. In the comparative analysis between the groups, it was found that the K^+ value was significantly higher in the I/R group than in the control, sham, and solvent groups (Mean differences = 1.778, SE = 0.192, 95% CI = 1.710-2.877, $P<0.001$). Renal function tests showed that TQ had a functional effect on the K^+ levels in renal I/R. Other parameters were not significant ($P<0.05$).

Melatonin and Ferritin Levels Associated with TQ Treatment

The significance between the groups was tested with One-Way ANOVA. Melatonin (SS = 3.204, df = 5, MS = 0.641, F = 351.960) and ferritin (SS = 3.745, df = 5, MS = 0.749, F = 24.847) levels were significant between the groups ($P<0.001$). Melatonin levels decreased in I/R injury, and an increase was detected after TQ treatment (Figure 2).

For melatonin, a statistically significant relationship was found between control, sham, and PBS with I/R and I/R+TQ. I/R and I/R+TQ showed significant relationships in all groups. Significance was also found between the TQ treatment group and the I/R and I/R+TQ groups (Table 1). Multiple comparative analyses demonstrated the functional effect of TQ on melatonin and ferritin levels. Ferritin levels were significant among control-I/R, sham-I/R, solvent-I/R, I/R-all groups, I/R+TQ-I/R and TQ-I/R ($P<0.001$). In the correlation analyses performed to determine the direction of significance, it was determined that melatonin and ferritin were in mutual interaction (Table 2).

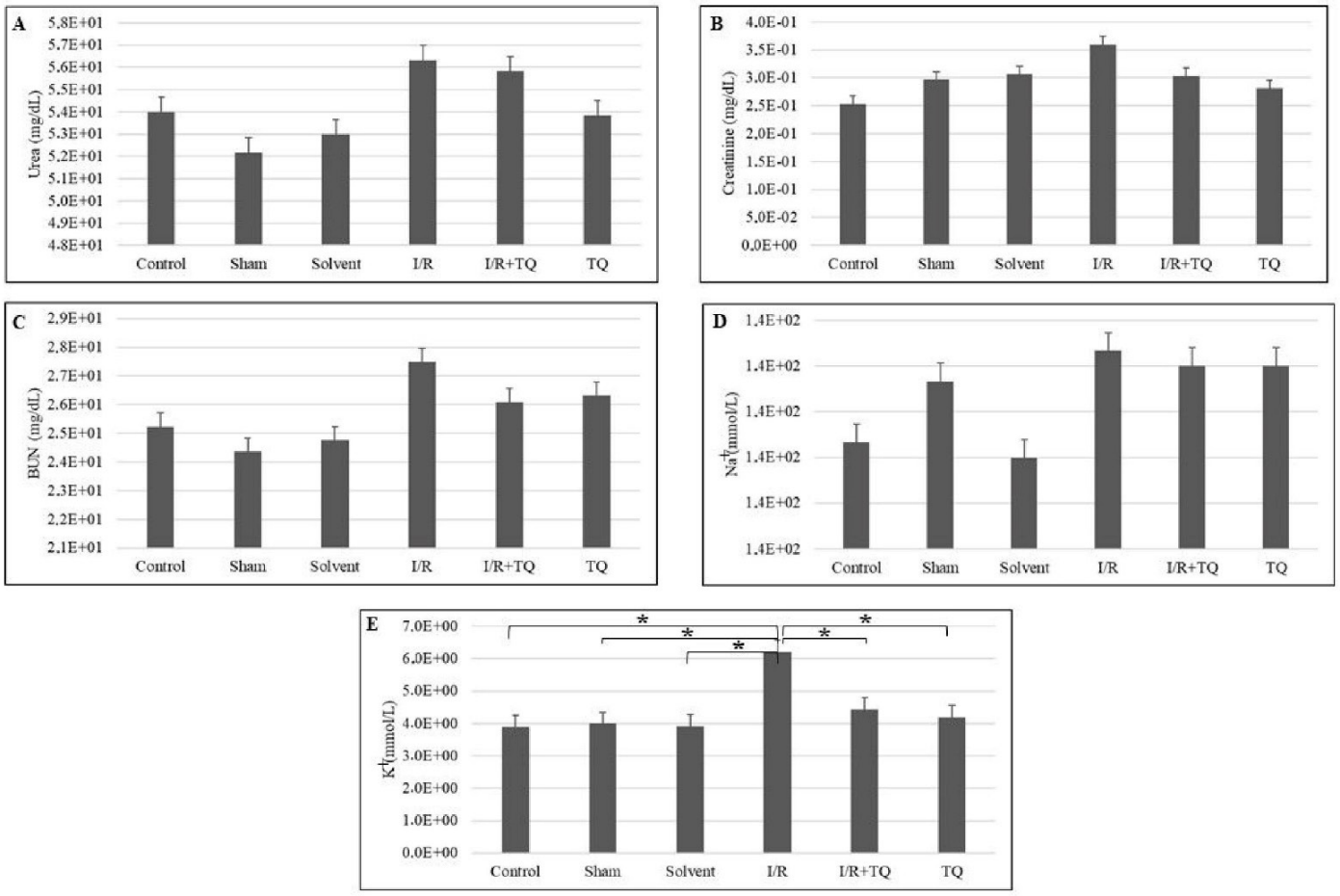

Figure 1. The serum levels of urea, BUN, creatinine, Na^+, and K^+ in the experimental groups. Error bars represent standard error. Urea, BUN, creatinine, and Na^+ were higher in the I/R group and lower after TQ treatment in all groups. The results were not statistically significant except for K^+. Potassium levels were significant in the I/R+TQ group compared to the I/R group. *P<0.05 is significant. **A.** Urea (mg(dL), **B.** Creatinine (mg/dL), **C.** BUN (mg/dL), **D.** Na^+ (mmol/L), **E.** K^+ (mmol/L).

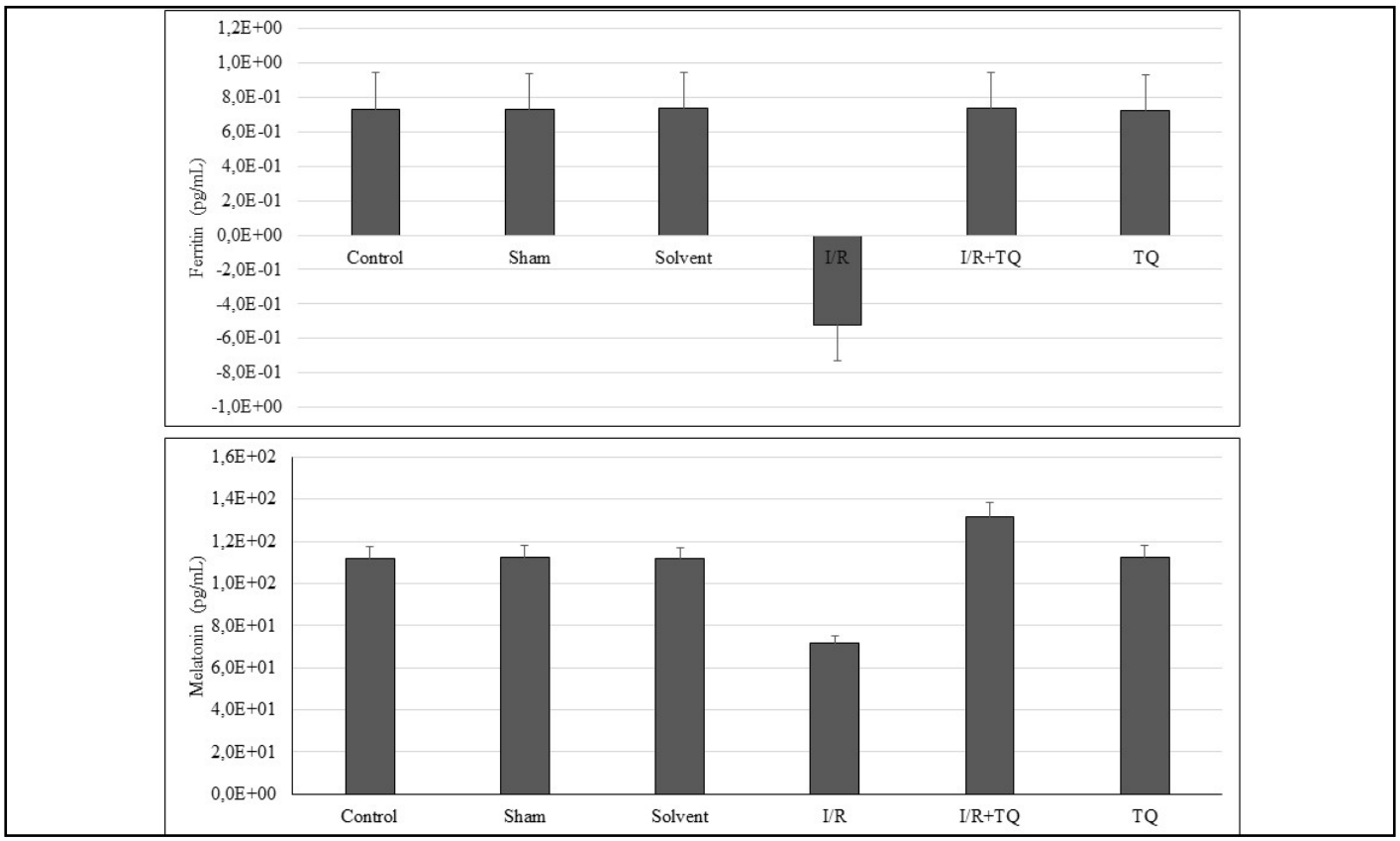

Figure 2. Renal tissue melatonin and ferritin levels in experimental groups. Melatonin levels were low after I/R injury in kidney tissue and increased after TQ treatment. Ferritin levels were high after I/R injury in kidney tissue and decreased after TQ treatment.

Table 1. Multiple comparisons of groups for kidney tissue melatonin and ferritin levels.

Parameters	Experimental Groups	Experimental Groups	Mean Difference	SE	P-value	95% CI
Melatonin	Control	Sham	-0.012	0.025	0.997	-0.087-0.063
		Solvent	0.001	0.025	1.000	-0.074-0.076
		I/R	0.661	0.025	**<0.001***	0.586-0.736
		I/R+TQ	-0.335	0.025	**<0.001***	-0.410--0.260
		TQ	-0.011	0.025	0.998	-0.086-0.064
	Sham	Control	0.012	0.025	0.997	-0.063-0.087
		Solvent	0.013	0.025	0.995	-0.062-0.088
		I/R	0.673	0.025	**<0.001***	0.598-0.748
		I/R+TQ	-0.323	0.025	**<0.001***	-0.398--0.248
		TQ	0.001	0.025	1.000	-0.074-0.076
	Solvent	Control	-0.001	0.025	1.000	-0.076-0.074
		Sham	-0.013	0.025	0.995	-0.088-0.062
		I/R	0.660	0.025	**<0.001***	0.585-0.735
		I/R+TQ	-0.336	0.025	**<0.001***	-0.411--0.261
		TQ	-0.012	0.025	0.996	-0.087-0.063
	I/R	Control	-0.661	0.025	**<0.001***	-0.736--0.586
		Sham	-0.673	0.025	**<0.001***	-0.748--0.598
		Solvent	-0.660	0.025	**<0.001***	-0.735--0.585

Melatonin		I/R+TQ	-0.996	0.025	**<0.001***	-1.071--0.921
		TQ	-0.672	0.025	**<0.001***	-0.747--0.597
	I/R+TQ	Control	0.335	0.025	**<0.001***	0.260-0.410
		Sham	0.323	0.025	**<0.001***	0.248-0.398
		Solvent	0.336	0.025	**<0.001***	0.261-0.411
		I/R	0.996	0.025	**<0.001***	0.921-1.071
		TQ	0.324	0.025	**<0.001***	0.249-0.399
	TQ	Control	0.011	0.025	0.998	-0.064-0.086
		Sham	-0.001	0.025	1.000	-0.076-0.074
		Solvent	0.012	0.025	0.996	-0.063-0.087
		I/R	0.672	0.025	**<0.001***	0.597-0.747
		I/R+TQ	-0.324	0.025	**<0.001***	-0.399--0.249
Ferritin	Control	Sham	0.005	0.100	1.000	-0.300-0.310
		Solvent	-0.001	0.100	1.000	-0.306-0.304
		I/R	0.867	0.100	**<0.001***	0.562-1.172
		I/R+TQ	0.000	0.100	1.000	-0.305-0.305
		TQ	0.007	0.100	1.000	-0.298-0.312
	Sham	Control	-0.005	0.100	1.000	-0.310-0.300
		Solvent	-0.006	0.100	1.000	-0.311-0.299
		I/R	0.863	0.100	**<0.001***	0.558-1.168
		I/R+TQ	-0.005	0.100	1.000	-0.310-0.300
		TQ	0.002	0.100	1.000	-0.303-0.307
	Solvent	Control	0.001	0.100	1.000	-0.304-0.306
		Sham	0.006	0.100	1.000	-0.299-0.311
		I/R	0.868	0.100	**<0.001***	0.564-1.173
		I/R+TQ	0.001	0.100	1.000	-0.304-0.306
		TQ	0.008	0.100	1.000	-0.297-0.313
	I/R	Control	-0.867	0.100	**<0.001***	-1.172--0.562
		Sham	-0.863	0.100	**<0.001***	-1.168--0.558
		Solvent	-0.868	0.100	**<0.001***	-1.173--0.564
		I/R+TQ	-0.868	0.100	**<0.001***	-1.173--0.563
		TQ	-0.861	0.100	**<0.001***	-1.166--0.556
	I/R+TQ	Control	0.000	0.100	1.000	-0.305-0.305
		Sham	0.005	0.100	1.000	-0.300-0.310
		Solvent	-0.001	0.100	1.000	-0.306-0.304
		I/R	0.868	0.100	**<0.001***	0.563-1.173
		TQ	0.007	0.100	1.000	-0.298-0.312
	TQ	Control	-0.007	0.100	1.000	-0.312-0.298
		Sham	-0.002	0.100	1.000	-0.307-0.303
		Solvent	-0.008	0.100	1.000	-0.313-0.297
		I/R	0.861	0.100	**<0.001***	0.556-1.166
		I/R+TQ	-0.007	0.100	1.000	-0.312-0.298

*The mean difference is significant at the 0.05 level. SE; standard error, CI; confidence interval.

Table 2. Correlation analysis of kidney melatonin and ferritin levels.

Parameters	Correlations	Melatonin	Ferritin
Melatonin (pg/mL)	Pearson Correlation	1	0.825*
	Sig. (2-tailed)		**<0.001***
Ferritin (ng/mL)	Pearson Correlation	0.825	1
	Sig. (2-tailed)	**<0.001***	

*Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

Hypoxic damage to the tissue resulting from ischemia results in the loss of cell integrity and ultimately cell death, depending on the duration of ischemia. In this process, the beginning of tissue reperfusion changes the extent of the damage. Free oxygen radicals released by polymorphonuclear leukocytes settling in the area after reperfusion increase tissue destruction and trigger reperfusion-related damage [14]. This defect may progress to acute kidney injury in the future. Renal function impairment is a known result of I/R. The underlying mechanism of this problem is inflammation-related. The inflammatory response in I/R further exacerbates the damage. Serum renal function tests can provide insight into the extent of the damage. In I/R, where optimal tissue oxygenation cannot be provided, suboptimal oxygenation cannot completely reverse the damage. This situation is reflected in serum markers and provides data about the onset of damage. These biological quantitative data are a signature of metabolic markers that compromise kidney function. Serum urea levels are filtered back to the plasma via the tubular epithelium and predict kidney disease as a clinical outcome by affecting factors such as the rate of hepatic production and protein intake [15]. Studies have determined that TQ reduces K accumulation in cerebral I/R [16]. In addition, TQ has a protective effect against toxicity caused by chemotherapeutic agents [17]. Among the urea, BUN, creatinine, Na^+, and K^+ used to analyze kidney functions, only K^+ was significant (Figure 1A-D). In terms of metabolic activities, potassium showed a more dominant difference in the groups. Renal excretion of potassium prevents toxic amounts from accumulating. A decrease in renal function is associated with increasing K^+ levels. In our study, TQ had no statistically positive/negative effect on parameters other than K in rats with I/R damage. At the same time, the obtained K^+ data suggest that TQ may have therapeutic potential in reducing elevated potassium levels in I/R.

Melatonin is a pineal hormone that is central to the biological clock and energy metabolism. Ferritin is an important protein that provides iron storage. As shown in this study, there is a metabolic link between the two molecules. Studies show that this link is achieved by triggering the degradation of ferroportin via hepcidin [18]. In this study, which showed that the molecular link is at the level of gene expression, it was shown that the expression of melatonin in hepatocytes induces hepcidin gene expression, promotes Fpn degradation, and thus causes cellular iron accumulation. In our study, we propose a mutual interaction between melatonin and ferritin in the renal tissue in I/R, similar to the regulation of iron homeostasis under the influence of melatonin in hepatocytes. Although an effect from melatonin to ferritin is suggested in hepatocytes, a flux from ferritin to melatonin may also be possible, as in our study. Ferritin is the only molecule taken up by the ferroportin receptor in cells. Its advantages and disadvantages are experienced in I/R. A previous study demonstrated that ferroptosis, a ferritin-dependent cell death mechanism, may be effective in reducing neuronal losses and regaining cognitive functions under the influence of TQ in a mouse Alzheimer's model [19]. Under normal conditions, the melatonin lost in the body can be compensated by other organs that adapt to the environment. A study has shown that iron overload. One study shows that iron overload reduces melatonin production [20]. In a recent study, melatonin was shown to be a ferroptosis inhibitor [21].

Limitations

The limiting factor in this study is that the effect on different organs in rats with a renal ischemia model was not demonstrated. Revealing the effects of the renal ischemia model on different organs in rats may contribute to the literature.

CONCLUSION

Our results indicate that TQ may affect both molecules separately or may play a role in the compensation of I/R damage by acting in the melatonin-ferritin direction or the ferritin-melatonin direction. TQ has the potential to a therapeutic in the regulation of I/R injury, and K^+ levels can be used as a marker in testing

renal function and response to treatment.

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Authors' contributions: Conception: ASB, ŞGY- Design: ASB., ŞGY. - Supervision: ASB., ŞGY. Fundings: ASB., ŞGY. Data Collection and/or Processing: ASB., ŞGY. - Analysis and/or Interpretation: ASB., ŞGY. - Literature Review: ASB., ŞGY. - Writing: ASB., ŞGY. - Critical Review: ASB., ŞGY.

Ethics approval: This study was approved by Gaziantep University Experimental Animals Local Ethics Committee (decision number:2024/49, protocol number: 398).

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Original Research

Awareness of Healthcare Faculty Students on Telehealth: A Mixed Methods Study

Didem Aytimur[1,*], Aliye Mandiracıoğlu[1], Ayşe Hilal Batı[2], Figen Gövsa[3]

[1] Department of Public Health, Faculty of Medicine, Ege University, İzmir, Türkiye
[2] Department of Medical Education, Faculty of Medicine, Ege University, İzmir, Türkiye
[3] Department of Anatomy, Faculty of Medicine, Ege University, İzmir, Türkiye

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Corresponding Author
Didem Aytimur, MD
Address: Department of Public Health, Faculty of Medicine, Ege University, Türkiye
E-mail: didem.aytimur@ege.edu.tr

ABSTRACT

Objective: The aim of the study is to determine the awareness and opinion of students in health professions' faculties about telehealth.

Method: This cross-sectional study was designed using a mixed methods approach including both quantitative and qualitative components. Seven hundred nighty seven second-year students from faculties of Medicine, Pharmacy, Dentistry and Nursing at Ege University were included in the study. A form including a section for personal information of the participants and items to determine students' awareness level on telehealth was created by researchers to collect quantitative data. The qualitative data were collected through semi-structured interviews with three students from each faculty selected by purposive sampling.

The relationship between responses to propositions and participants' socio-demographic characteristics was evaluated using t-test and ANOVA. Chi-square tests were used to evaluate other characteristics of the students according to their schools and their responses to propositions about telehealth. For qualitative data, manual descriptive analysis was used. Interview transcripts were read by two researchers, code was assigned to each concept, and they were grouped under thematic headings.

Results: Of the participants, 28.8% reported that they have already heard of the term telehealth. Students are much less familiar with the terms of telenursing and teledentistry. The average total awareness score of the students was 12.70±7.27 [0-27].

Conclusion: Majority of the students are found to lack sufficient awareness of telehealth. This outcome highlights importance of determining awareness levels of future healthcare professionals, who will use these services in their professional lives; especially given that telehealth services have begun to be used widely around the world and have become legally regulated in our country. It points out the necessity of receiving education on this topic during undergraduate period.

Keywords: telehealth, medical students, dentistry students, nursing students, pharmacy students

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INTRODUCTION

Telehealth is commonly used as an "umbrella term"; encompassing education, research, health surveillance, and promotion, in addition to the delivery of healthcare services. The pressures arising from these factors on service delivery have prompted healthcare providers to seek innovative solutions. Telemedicine refers to the use of communication networks to provide healthcare services remotely [1]. The World Health Organization (WHO) defines it as ''the delivery of health services where distance is a critical factor, by all health professionals using information and communication technologies, for the diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and the exchange of valid information for continuing education of health service providers'' [2,3].

Telemedicine offers a novel approach to the provision of healthcare services across different geographic regions with limited access to facilities [4,5]. There is a significant need to ensure that students in healthcare-related educational institutions should be competent in telehealth applications at the point of graduation. Among the barriers to the integration of telehealth into healthcare services, the absence of education covering telehealth topics in faculties is a notable deficiency. Nowadays, the support of traditional face-to-face healthcare services with virtual and electronic applications seems inevitable. It becomes increasingly important for students to learn how to manage these new applications, enhance their digital literacy, and be prepared for post-graduation working conditions [6,7,8]. Various remote health applications in Türkiye have been introduced during COVID19 pandemic period like e-Nabız [9].

Successful implementation and maintenance of telemedicine in healthcare depend on the competence and efficiency of the medical professionals using the technology. However, very little is known about the opinions, awareness, skills, and training of our future healthcare providers regarding this issue. Undoubtedly, the younger generation, considered the first cohort of 'digital natives,' possesses more expertise in technology compared to the older generation. As medicine continues to integrate technology into patient care, it is crucial for medical schools to introduce students to the technological methods they will use in the future and ensure that they understand and analyze the advantages and disadvantages of these methods [1,5,10,11]. Therefore, it is first necessary to evaluate how much future healthcare professionals know and apply the technologies that are predicted to be used more frequently.

The aim of the study is to determine the awareness and opinions of students, who are the future healthcare professionals, regarding telehealth, a technological method that is becoming increasingly prevalent in patient care.

Main Points

- Fewer of the students reported that they have already heard of the term telehealth. Students are much less familiar with the terms of telenursing and teledentistry.
- Considering that this practice will also become widespread in Türkiye in the very near future; it is clear that there is a need for immediate action in this area, thus it is necessary to receive education on this topic during the undergraduation period of the health sciences students.

MATERIALS AND METHODS

Setting: This cross-sectional study was designed using a mixed methods approach including both quantitative and qualitative components. Health professions' faculties available at Ege University are; medicine, dentistry, nursery and pharmacy. Yet there is no telehealth related content in the curricula of these faculties.

Study Design and Flow

Data was collected voluntarily, at lecture halls where students are gathered together, at the beginning of the academic year of 2024 spring and at the end of the courses in second year students of the four faculties mentioned, under the control of faculty members in the research group. The survey forms were applied anonymously. Verbal and written consent of students participating in the study were taken.

Participants: A total of 1,330 second year students from the faculties of Medicine (430), Pharmacy (170), Dentistry (250), and Nursing (480) at Ege University were planned to be included in the study. Using the EPI INfo 7.0 program for the sample, it was calculated that at least 434 students should be included in the study, taking the frequency of hearing the term telehealth as 41% (12) and the confidence interval as 99%. These students are the group of students who have not yet progressed to the clinical stage and are generally taking basic courses. In addition, it was preferred that the faculty members in the research team

teach these classes, as this will facilitate accessibility to students and the execution of the project. The inclusion criteria are; to be a second-year student studying in one of the faculties of Medicine, Nursing, Dentistry and Pharmacy at Ege University and volunteering to fill out the survey form. Students who did not attend school during the data collection period and if there was missing information in the survey forms to be collected anonymously from students, those students were excluded from the study.

Data collection tools: A form including a section for personal information of the participants and items to determine students' awareness level on telehealth was created by researchers to collect quantitative data. This form was delivered to all students. Out of these, 797 students (60.1%) voluntarily completed the survey forms and formed the study group. A questionnaire was prepared to collect data on students' school, gender, level of awareness on science and technology, desire to receive education on telehealth, and post-graduation career plans. To assess students' level of awareness on telehealth, a 27-item form created by researchers in line with the literature was used. Each item had the options "Yes," "No," and "I don't know," with "Yes" answers scoring 1 point and both "No" and "I don't know" responses scored as 0, from which a total score was calculated. The maximum score was 27.

Ethical considerations: The study was ethically approved by the Ege University Faculty of Medicine Medical Research Ethics Committee (30.11.2023, 23-11.2T/42). Permission to collect data was obtained from all faculty administrations within the scope of the survey.

Data Analysis

This study employs both qualitative and quantitative methods for triangulation. This approach enhances the strength of the results and allows for the discovery of potentially overlooked information by integrating multiple research types. The quantitative section of the study identifies participants' awareness levels and related factors regarding telehealth, while the qualitative section provides a more detailed understanding of participants' perspectives. Structured questions were used in the qualitative research section during interviews. Additionally, if new relevant topics emerged, the opinions of all participants on these issues were also taken into consideration. Focus group discussions and qualitative research are dynamic processes where uncertainties and new situations are resolved throughout the process [13,14].

For qualitative interviews, purposive sampling was used to select three students from each faculty. This sampling technique was preferred because it had allowed the selection of individuals who could better express their awareness about telehealth, their personal experiences and opinions on telehealth applications. The data for the qualitative study were collected using a semi-structured interview form consisting of four main open-ended questions and sub-questions probing for details. The questions posed to the students were:

- How do you relate to technology? We started using electronic infrastructure more during the pandemic and subsequently the earthquake period; what technologies have entered your life in this period?
- What do you know about telehealth?
- What are your thoughts on the effectiveness of telehealth applications?
- What are your thoughts on including telehealth and related topics in the curriculum of your faculty?

A total of four focus group discussions were conducted, each lasting between 30-40 minutes. The discussions were carried out by experienced researchers. Each discussion began with an explanation of the study's purpose and the obtaining of informed voluntary consent.

Quantitative data analysis was performed using SPSS 23.0. Initially, all variables were subjected to a normal distribution fit test, and the suitability to parametric test criteria was assessed. The relationship between responses to propositions and participants' socio-demographic characteristics was assessed using t-test and ANOVA. Benforini tests were used for post hoc analysis. Moreover, chi-square tests were used to evaluate other characteristics of the students according to the schools they attended and their responses to statements about telehealth. For the analysis of qualitative data, manual descriptive analysis was utilized. All interview transcripts were read separately by two researchers, after which common and differing concepts were identified, a code was assigned to each concept, and the codes were grouped under thematic headings. In selecting quotes from participants' opinions, expressions that were frequently repeated or unique, as well as those that were contrasting or not similar, were considered. Quantitative and qualitative data were interpreted together.

The study was ethically approved by the Medical Research Ethics Committee of Ege University Faculty of Medicine (30.11.2023, 23-11.2T/42). Permission to collect data was obtained from the administrations of all faculties involved in the research.

RESULTS

Of the study group, 61% were female, and 76.2% were aged 20 and below, with the majority indicating their intention to pursue further education through master's or specialty training after graduation. The characteristics of the students are presented in Table 1.

Table 2 displays the characteristics of students and the statistical differences according to faculties. The majority of students in the nursing faculty were female. The awareness levels about telehealth among medical students were assessed to be poorer compared to other faculties. The students from the nursing faculty were more eager to receive information about telehealth.

28.8% of the students participating in the study have reported having heard of the term telehealth. The students were much less familiar with terms such as telenursing and teledentistry (Table 3).

The average total awareness score of the students was 12.70±7.27 [0-27] Pharmacy faculty students; were mostly female students; those with a good perception of telehealth awareness and willing to receive telehealth education. They believed that telehealth topics should be included in the curriculum. They had statistically significantly higher awareness scores when compared to the other faculties (Table 4).

Qualitative Findings

The qualitative findings were examined under three thematic headings: students' awareness and use of technology, their awareness of telehealth, and their perceptions of the place of telehealth in undergraduate educational programs.

Theme1: Technology Use and Familiarity

Students participating in the interviews were from various cultures, cities and had succeeded in entering Ege University from schools with different educational methods. They mentioned they had used computers and internet technologies for purposes such as gaming, communication, preparing homework and had got acquainted with teleconference applications [like Zoom, Teams] during the remote education sessions conducted after the pandemic and the major earthquake disaster in Türkiye. Some of the student statements within this theme were as follows:

Medical student 1 (male): "We hardly experienced any technical problems during this period."

Pharmacy student 1 (male): "I feared that school might continue online for a long term because I feel I learn less without the compulsory attendance and coming to school increases discipline."

Nursing student 1 (female): "We manage everything on our phones. we even downloaded 3D applications to study for anatomy classes."

Dentistry student 3 (female): "Not only us but also educators need to be aware of this issue and equipped in this area."

Table 1. Characteristics of Students

Characteristics	Number	%
Faculty		
Dentistry	143	17.9
Pharmacy	157	19.7
Nursing	258	32.4
Medical School	239	30.0
Gender		
Female	487	61.0
Male	310	38.8
Age Group		
20 and under	609	76.2
21+	188	23.5
Awareness of Telehealth		
Poor	116	14.5
Medium	561	70.2
Good	**117**	14.6
Desire to Receive Telehealth Education		
Yes	464	58.1
No	325	40.7
Opinion on Including Telehealth in the Curriculum		
Should be included	613	76.7
Not necessary	174	21.8
Career Plan		
Post-Graduation Work	235	29.4
Specialization	386	48.4
Academic Education	107	13.4
Other	8	1.0

Table 2. Some Characteristics of Students and Their Awareness about Tele-Health According to Faculties

Characteristics	Faculty				Total	Chi-square, p
	Nursing	Medicine	Dentistry	Pharmacy		
	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	
Gender						
Female	211 (81.8)	106 (44.4)	73 (51.0)	97 (61.8)	487 (61.1)	80.755
Male	47 (18.2)	133 (55.6)	70 (49.0)	60 (38.2)	310 (38.9)	**0.001**
Awareness of Telehealth						
Poor	34 (13.3)	49 (20.5)	15 (10.5)	18 (11.5)	116 (14.6)	15.787
Medium	188 (3.7)	151 (63.2)	112 (78.3)	110 (70.1)	561 (70.7)	**0.015**
Good	33 (12.9)	39 (16.3)	16(11.2)	29 (18.5)	117(14.7)	
Willingness to Receive Education on Telehealth	182 (71.7)	109 (46.0)	65 (45.5)	108 (69.7)	464 (58.8)	51.458 **0.001**
Heard of Telehealth	58 (22.5)	58 (24.4)	33 (23.1)	81 (50.9)	230 (28.8)	47.58 0.001
Heard of Telemedicine	32 (12.4)	45 (19.1)	26 (18.4)	47 (29.6)	150 (18.9)	18.92 **0.001**
Heard_of Telenursery	25 (9.7)	16 (6.8)	11 (7.7)	17 (10.7)	159 (8.7)	2438 0.49
Heard of Teledentistry	16 (6.2)	15 (6.3)	22 (15.4)	13 (8.2)	66 (8.3)	12.21 **0.007**
Heard_of Telepharmacy	16 (6.2)	18 (7.7)	12 (8.4)	35 (22.3)	81 (10.3)	31.16 **0.001**

Table 3. Students' Responses to Statements (%) about Telehealth

Statements	Agree %	Disagree %	Unsure %
1. I have heard of the term telehealth before	28.8	56.8	14.4
2. I have heard of the term telemedicine before	18.9	66.1	15.0
3. I have heard of the term tele-nursing before	8.7	75.4	15.9
4. I have heard of the term tele-dentistry before	8.3	75.8	15.9
5. I have heard of the term tele-pharmacy before	10.3	73.0	16.8
6. Telehealth is the use of telecommunications to provide health information and services	51.9	6.8	41.3
7. Telehealth requires performance tools and a strong internet infrastructure	57.0	6.5	36.6
8. Telehealth can apply treatment management strategies like physiotherapy. psychotherapy. and medication therapy	44.8	11.9	43.3
9. Health consultancy can be provided through telehealth applications	65.2	4.2	30.7
10.Patient examinations can be evaluated and monitored through telehealth	60.5	7.2	32.3
11.Telehealth is a good alternative in situations where access to healthcare institutions is difficult	68.0	4.0	28.0
12.Using telehealth in situations that require face-to-face consultation with the patient can create risks	55.9	8.9	35.2
13.Telehealth services shorten the waiting time	63.8	4.7	31.5
14.Telehealth alone is an effective method for solving all kinds of health problems	10.5	60.1	29.5
15.Telehealth services are initiated after a face-to-face meeting	33.9	10.0	56.1
16.A face-to-face meeting may be required after telehealth service	61.9	3.8	34.3

17.Telehealth reduces direct contact between healthcare workers and patients	64.8	6.3	28.9
18.Telehealth applications allow for effective time use for both healthcare workers and patients	67.9	4.2	27.9
19.Telehealth can be widely used in general practitioners' monitoring of chronic diseases/pregnancy/ infant/child/vaccinations	48.2	11.0	40.8
20.Telehealth applications can be effectively used in individual and community health education	64.4	6.6	29.0
21.Telehealth can be used more widely in extraordinary situations like the Covid-19 pandemic	68.9	3.7	27.4
22.Telehealth applications can transmit images related to the disease using digital cameras, mobile phones etc.	63.3	6.3	30.4
23.Electronic patient monitoring devices such as blood pressure monitors and thermometers can be used in telehealth applications	30.2	21.1	48.7
24.Telehealth applications are reliable in terms of respecting patient confidentiality and protecting personal data	38.1	14.9	47.0
25.The use of telehealth strengthens communication between healthcare professionals and patients	43.9	19.3	36.7
26.Telehealth applications can reduce healthcare costs	62.0	5.7	32.3
27.Telehealth applications will become more widespread in the future	69.4	3.3	27.3

Table 4. Telehealth Awareness Scores According to Certain Characteristics of Students

	Awareness Score Mean±SD	**t-test/ANOVA**
Faculty		
Dentistry	13.27±6.87	F:6.79 P:0.001
Pharmacy*	14.81±6.82	
Nursing	11.57±7.47	
Medical School	12.08±7.29	
Gender		
Female*	13.10±6.84	t:3,955 p:0.045
Male	11.97±7.88	
Age Group		
20 and under	12.73±7.22	
21+	12.50±7.42	
Awareness of Telehealth		
Poor	9.31±7.10	F:12.609 P: 0.001
Medium	13.03±7.21	
Good*	13.93±6.91	
Willingness to Receive Education on Telehealth		
Yes*	13.39±7.12	t:2.905 p:0.004
No	11.78±7.36	
Opinion on Including Telehealth in the Curriculum		
Should be included*	13.34±7.12	t:3,955 p:0.001
Not necessary	10.75±7.24	

(*)Pharmacy faculty students, female students, students with good awareness of telehealth, students that want to receive education on telehealth and students that want telehealth to be included in curriculum are the groups found to make the difference

Theme 2: Opinion on the Awareness and Effectiveness of Telehealth

The students interviewed did not have sufficient awareness about telehealth. They believed that telehealth applications could not replace traditional medical consultations involving touch and face-to-face communication. They acknowledged that telehealth could facilitate some aspects for doctors and patients also supported the idea that telehealth could be very beneficial for older individuals and patients requiring monitoring for chronic diseases as it could reduce transportation costs and prevent waiting in crowds at healthcare institutions. Additionally, they mentioned that telehealth applications could reduce the physical burden on the institutions providing the service and prevent unnecessary emergency room visits. On the other hand, they also discussed the limitations of telehealth applications; emphasizing issues such as the need for technical infrastructure and the ability to use technological tools. It was pointed out that older individuals and people living in socioeconomically disadvantaged areas of Türkiye might not have the infrastructure or the capability to use this technology. It was also highlighted that making healthcare services more accessible and easier, could lead to overuse and strain on the system or cause problems in their own treatment processes. The students emphasized on the need to paying attention to issues like the privacy of personal data. Student statements related to this theme included:

Medical student 2 (female) "It could be possible in some specialties. for instance; it would be very useful for psychiatry. Consulting could be provided. For example, if someone has complaints, should they visit a hospital or can it be resolved on their own?"

Pharmacy student 3 (female): "For patients with chronic diseases using it for things like prescription refills would be very functional; saving both time and money. I don't think it would be feasible in dentistry or nursing. It's not suitable for psychiatry or general surgery. Examination or close consultation is essential."

Nursing student 1 (female): "Some home visits by nurses could be done via telenursing saving the nurse's time and strengthening the patient-nurse connection by allowing more frequent communication with the community they serve."

Dentistry student 2 (male): "In an emergency; if a child loses a tooth from a fall we can advise the parent not to throw the tooth away. It can be very beneficial like teaching how to brush teeth for preventive oral, dental health. Not suitable for all areas of dentistry. Could be used for monitoring in orthodontic treatment."

Theme 3: Telehealth Education in Undergradute Curriculum

The students in focus group discussions, agreed that these topics should be included at some stage of their education. It has also been mentioned that; it could be used as a method to enhance professional experience at their postgraduate period. Some examples of student statements related to this theme are:

Medical student 2 (female): "I think it should be included in specialty training; it's too early for medical education."

Pharmacy student 1 (male): "It might be an elective or compulsory course. or information on this topic might be included within a course."

Nursing student 1 (female): "It might be an elective course. or it might be included in the program without increasing our course load."

Dentistry student 1 (female) "It might be included in our curriculum. If we are going to use these services when we graduate, we should start learning about them now. We wouldn't want our curriculum to include topics that won't be useful after graduation."

DISCUSSION

It's the first study in Türkiye to investigate healthcare students' awareness on telehealth. The majority was found to lack sufficient awareness of telehealth. This outcome highlights the importance of determining the awareness levels of future healthcare professionals, who will use these services in their professional lives; especially given that telehealth services have begun to be used widely around the world and have become legally regulated in Türkiye. It points out the necessity of receiving education on this topic during the undergraduate education period. Educators, who are digital immigrants and were introduced to technology in later stages of their life, might have limited use of these technologies. The literature emphasizes the importance for the younger generation described as digital natives to be familiar with the healthcare technologies they will use in the future. to analyze and understand the advantages and disadvantages of these methods and to become proficient in using them comfortably through experiences during their education [1,5,10,11].

According to the results of this cross-sectional study; of the participants, 28.8% reported having heard of the term telehealth, while significantly fewer students were familiar with terms like telemedicine, telenursing, teledentistry and telepharmacy. As determined in the qualitative part of the study; it is clear that students were not aware of these terms. Studies with medical students have shown that between 41.5% and 86.9% of students reported having heard of the terms telehealth and telemedicine [15,16,17]. In Indonesia, it was reported that only a quarter of pharmacy students were aware of telepharmacy applications [18]. The literature shows that awareness of teledentistry among dental students ranges from 17.2% to 79.1% [19,20,21]. Another study reported that 82% of nursing students were aware of telemedicine while only 75.2% were aware of telenursing [22].

In this study; pharmacy students were found to be more likely to believe they had good awareness of telehealth. On the other hand, the eagerness to learn about this topic was observed more among nursing students. A study in the USA reported that 35.2% of medical students believed that the topic of telemedicine should be included in the curriculum [23]. In Poland, 69.5% and in Iran 72.3% of nursing students expressed their desire to see telenursing topics in their courses [22,24]. Another study reported that 71.2% of students believed that teledentistry should be included in the curriculum [21]. Researchers worldwide emphasize the necessity of including these topics in the curricula of all faculties training health personnel [11,25,26,27]. By including the topics in the curricula for instance familiarizing trainees with telemedicine practices might enhance their confidence and proficiency, leading to a more favorable learning experience [28].

It is striking that the awareness of Ege University students about increasingly popular telehealth applications is much lower compared to many countries. Considering that this practice will also become widespread in Türkiye in the very near future; it is clear that there is a need for immediate action in this area.

According to the quantitative results of the study the propositions that students most agreed upon are that telehealth applications will become more widespread in the future, can be more commonly used in extraordinary situations such as COVID19 pandemic, serve as a good alternative in situations; where access to healthcare institutions is difficult, and reduce waiting times to take healthcare. The outcome of the qualitative study also support these results. Many countries report that telehealth applications may be an alternative for the increasing homecare needs of elderly population and may direct patient care services at home [4,20,29]. In group discussions of the study, students mentioned that telehealth services might be used for on-line self-diagnosis and triage. Similarly, more than half of the medical students in China reported that telemedicine services might be used for the same purposes [15]. On the other hand; in focus group discussions, students anticipated possible barriers to the use of telehealth, those lacking technological infrastructure, awareness, skills to use it would not be able to benefit from these services [14]. Additionally; it was argued that information, communication technologies provide an opportunity for developing countries effectively reach vital development goals such as reducing poverty, basic healthcare services, and education [30].

Malhotra et al, reported that students taking clinical courses are generally more aware of telemedicine than other students [4]. Another study reported that nursing students with clinical experience had higher levels of telenursing awareness [31]. Ellatif et al, found that 35,5% of nursing students had a good level of awareness about telenursing [32]. It becomes evident that these students, who will be part of the future healthcare team, need to be prepared for future service models before graduation.

According to the quantitative results of this study, pharmacy students, female students, those with a good awareness of telehealth, those interested in receiving telehealth education, and those believing that telehealth topics should be included in the curriculum, statistically have higher awareness scores regarding telehealth. These results indicate that students are interested in the topic, are more eager to learn. Although our study found that female students were more interested, the literature suggests that the relationship between students' telehealth awareness and their demographic characteristics may be coincidental as some studies did not find a significant association [4,31,33]. A study involving medical faculty staff and students found lower telemedicine awareness among students [34]. Conversely; a study with medical students showed that those who had received education on telemedicine or believed in the necessity of such education had better telehealth awareness [35].

Limitations and Strengths of the Study

The study is limited as being conducted at a single university and the sample scope is restricted to only second year students that have not yet taken a course on this subject until this grade. The

outcome of the study is not generalizable as the cross-sectional nature of it; limiting the ability to explain causality, and the reliance on student self-reports. On the other hand, it is the only study in Türkiye conducted with the participation of students from pharmacy, nursing, dentistry, and medical faculties simultaneously. Since the form used for the cross-sectional study was not intended as a scale, validity and reliability analyzes were not performed. It may be considered as the validity evidence of the data collection tool is limited. Therefore, we recommend future studies to use validated data collection tools. It is one of the few studies in the literature that examines telehealth from the students' perspective. The use of both qualitative and quantitative methods strengthens the results. The combination of quantitative and qualitative methods is important for accessing information that might be overlooked when using only one type of research and for enhancing the strength of the finding. While the quantitative part of the study identifies the awareness status of participants on telehealth and related factors, the qualitative part guides a more detailed examination of participants' perspectives. Considering the limited literature in this field, we believe this study will provide useful information and guidance for educators and policymakers in pharmacy, dentistry, nursing and medical education. Developing and enhancing educational programs that include telehealth will accelerate high-quality, safe practices.

This study found that only one-third of students had heard of the term telehealth; even fewer were aware of telepharmacy, telenursing, teledentistry. It is necessary that educational programs in all faculties offering health sciences education support theoretical lessons with applications and include clinical practices open to student participation. The fact that the study group consisted of students (second grade students) who have not yet taken clinical courses and that none of the four faculties' curricula currently include telehealth could be the reason for this result. Conducting telehealth applications in environments with legal regulations for personal data protection, similar to councils with doctors from different disciplines, will lead to beneficial outcomes for patients and strengthen collaboration among physicians. Discussions bringing together different health professional groups could also be conducted. These environments will offer unique experiences for students, providing opportunities to learn in real-life settings, evaluate and understand topics from different perspectives. Considering the active use of artificial intelligence in professional practices, absence of telehealth in educational curriculum should be seen as a significant deficiency.

CONCLUSION

Majority of the participants exhibited inadequate awareness of telehealth in this study. This emphasizes the importance of assesing the awareness levels of prospective healthcare practitioners, who will integrate these services into their professional domains. This is particularly crucial as telehealth services are increasingly adopted globally; consequently, there is an emerging need to incorporate telehealth education into the undergraduate curriculum.

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

Informed Consent: Informed consent document was obtained from the study participants.

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Original Research

The Effects of Hands-on Cadaver Dissection Module on Preclinical Students

Serdar Babacan[1, *], Devran Çitak[2], Mustafa Deniz[3]

[1] Department of Anatomy, Bursa Uludag University, Faculty of Medicine, Bursa, Türkiye
[2] Harran University, Faculty of Medicine, Şanlıurfa, Türkiye
[3] Department of Anatomy, Harran University, Faculty of Medicine, Şanlıurfa, Türkiye

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Corresponding Author
Serdar Babacan, MD
Address: Department of Anatomy, Medical Faculty, Bursa Uludağ University, Bursa, Türkiye
E-mail: sbc010777@gmail.com

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ABSTRACT

Objective: The anatomy education provided by cadaver dissection contributes to the professional skills of medical students. In addition to gaining scientific experiences, dissection practices contribute to the humane approach to the patient, motivation to become a physician, privacy, and ethical issues. Cadaver dissection is one of the oldest methods used in anatomy education, and the moment of encounter with the cadaver significantly affects medical students. The aim of the study was to emphasise the importance of traditional cadaver dissection and raise awareness about body donation.

Methods: The study included 206 preclinical period students. After receiving the dissection materials, the students dissected cadavers, and the instructors helped them throughout the process. After the dissection, we shared an online survey.

Results: 96.6% of the students emphasised that cadaver dissection is important and should be included in the curriculum. Also, 96.6% stated that the dissection module informed them about ethical values. 94.2% declared that dissection increased their interest and motivation towards medical education. 91.8% of the students thought that participation in cadaver dissection provided them with more opportunities to develop professional skills than the demonstration of a prosectioned (previously dissected) cadaver. 71.8 of them stated that the models or computer-assisted education can not replace cadaver dissection.

Conclusion: However, although technology and artificial intelligence facilitate learning, the multifaceted benefits of the cadaver cannot be denied, and the cadaver cannot be excluded from anatomy education.

Keywords: Cadaver dissection, Anatomy education, Cadaver and ethics, Medical education

INTRODUCTION

There are many different reasons why students choose medicine. These include those who choose medicine by their own choice, as well as those who do so on the recommendation of their family, and those who are influenced by social media. Of the hundreds of medical students who come together with different motivations, very few have any idea how to adapt to their new role as a medical student. This is why dissection rooms

in anatomy departments serve as the first bridge between the public and the medical world for beginner medical students [1].

The science of anatomy, which examines the morphological characteristics of the body and organs, structural and functional relationships between organs, is known as the cornerstone of preclinical medical education [2,3]. Historically, cadaver dissection has been an important experience as a basic teaching tool in gross anatomy education for centuries and has formed a vital part of medical education [4-7]. The cadaver in anatomy education is the "first patient" and "first teacher" of a medical student. The "student-cadaver" interaction is very important as it is the first simulation of the "physician-patient" relationship [8-11].

There is a divergence of opinion between proponents of traditional anatomy and proponents of technology-assisted anatomy education. [12-14]. The worldwide trend in medical education is characterized by a shift towards student-centered, integrated, clinical practice models [9]. As a result, there has been a significant reduction in the amount of time devoted to cadaver dissection. This has significantly reduced the time allocated to traditional cadaver dissection [15,16]. However, cadaver dissection in the anatomy curriculum is important not only to learn anatomical structures in depth in three dimension but also to solve psychosocial problems that may be an obstacle to medical science [13,17].

Cadaver dissection is very important for medical students in terms of learning the three-dimensional relationships of anatomical structures comprehensively in understanding the human body [3,6,18,19]. In this context, studies have shown that cadaver dissection is a vital part of medical education to provide future physicians with anatomy knowledge that they can rely on throughout their careers [4,20,21].

Main Points

- Taking photos/videos with cadavers and sharing photos/videos on social media is not appropriate in terms of medical ethics
- Hands-on dissection module increases the sense of gratitude towards people who donated their bodies to medical education
- The hands-on dissection module increases the interest and motivation towards medical education and the profession of medicine
- Approaching the cadaver is as sensitive and important as approaching the patient

Cadaver dissection is the basis for students to put theoretical knowledge into practice and understanding patients, establishing an emotional relationship with patients psychologically, balancing sensitivity and impartiality, and developing ethical values related to death and the human body [21-28]. Cadaver dissection is the basis for students to transfer theoretical knowledge to practice, to get used to working with a team, to learn to work in a disciplined manner, to develop manual skills, strategies to cope with stress and time management [20,29,30]. In short, the acquisition of the best professional principles, attitudes, expertise and behaviour starts from the first day of medical school and continues throughout the entire professional life. Cadaver dissection has a crucial role in attaining these acquisitions [25].

The study aimed to investigate the psychological effects of the cadaver dissection module on preclinical students in addition to anatomy education, to emphasise the importance of traditional cadaver dissection in medical faculties against developing technological materials, to raise awareness about body donation, to increase students' motivation to be a medical student and physician during distance education applied in situations such as disasters and pandemics.

MATERIALS AND METHODS

The study included preclinical period students studying at Harran University Faculty of Medicine. A total of 131 (63.6%) 1st year students, 49 (23.8%) 2nd year students and 26 (12.6%) 3rd year students participated in the study. 90 (43.7%) male and 116 (56.3%) female students participated in the study. The approval decision numbered HRU/22.08.11 was obtained from the Harran University Clinical Research Ethics Committee for the study. In the online surveys, voluntary consent was first obtained. After they accepted the study by pressing the voluntary consent button, they could see the questions.

Design of the Practical Dissection Module

We divided the preclinical students into groups of ten and included them in the study. After determining the groups, we created a calendar for the application and announced it to the students. We determined the dissection time for each group as 2

hours. Before taking the students who would participate in the dissection into the hall, we asked whether they were hungry, and whether they had complaints such as dizziness or nausea. We made explanations about what a cadaver is and how it can be obtained. We answered the questions they were curious about. We made explanations about the cadaver dissection hall, explained the rules to be followed. We made them sign the document that they accepted the rules to be followed in the cadaver dissection hall. After entering the dissection hall, we opened the cadaver and introduced them to the cadaver. After waiting for them to get used to it for a while, we described the materials to be used in dissection and how to use them. After making explanations about the materials, we divided the students into groups of two. We distributed the student groups to 5 regions of the cadaver: head-neck, upper extremity, lower extremity, abdomen and thorax. We explained which anatomical structure (skin, fascia, subcutaneous adipose tissue, muscle, vessel, nerve, organ, etc.) should be dissected by showing how to dissect. The students started dissection after receiving the dissection materials and the instructors helped them throughout the process. After the dissection period was over, we gave suturing training.

Administering the Questionnaire

After the cadaver dissection, we shared the link to the online questionnaire with the participants. We asked them to answer the questions without changing their psychological state after dissection. Sociodemographic questions were the first in the survey questions. Then there were 24 questions in the form of a 5-point Likert scale by the researchers. We determined the scoring of the answers to the questions as strongly disagree (1); disagree (2), undecided (3); agree (4); strongly agree (5).

Statistical Analysis

We performed statistical analyzes using IBM SPSS version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). We performed frequency analysis for categorical variables. For the descriptive statistics of the variables, we analyzed the mean ± standard deviation values. For the normality test of the distribution of the variables, we applied the Shapiro Wilk test. For the comparison of paired groups, we used the independent sample t-test (Student's T test) for normally distributed variables and the Mann Whitney-u test for variables not normally distributed. We considered the statistical significance level as $p<0.005$.

RESULTS

The mean ages of 90 (43.7%) male and 116 (56.3%) female students were 20.33 ± 1.98 and 19.94 ± 1.17 years, respectively. 89.9% (n=185) of the participants stated that it was their choice to study medicine, while 10.2% (n=21) stated that it was not their choice to study medicine. 88.8% (n=183) of the volunteers stated that they were interested in medical education, while 11.2% (n=23) stated that they were not interested in medical education.

The frequency distributions of the answers given by the participants to the survey questions and the mean ± standard deviation values of the scores resulting from the scoring of the answers given are shown in Table 1.

In the normality test, we found that none of the variables were normally distributed. As a result of the comparative statistics (Mann Whitney-U test) between those who had seen cadavers before and those who had not seen cadavers before, we did not find a statistically significant difference between the groups in any question. Similarly, as a result of the comparative statistics (Kruskal-Wallis test) between the period 1, period 2 and period 3 groups, we did not find a statistically significant difference between the groups (Table 2).

DISCUSSION

The importance of cadaveric anatomy education in the medical curriculum is undeniable. For centuries, cadaveric training has been recommended as the cornerstone of anatomy education. This study demonstrated that cadaveric anatomy training has advantages over other methods and that learning anatomy by dissecting the cadaver with a hands-on method is superior to learning anatomy on a previously dissected cadaver. He also expressed the opinion that cadaver dissection is very important not only for anatomy education but also for increasing the motivation of physician candidates who have just started medical education and for the beginning of medical ethics gains.

Table 1. Frequency distribution and descriptive statistics values of the answers given to the survey questions.

Questions	1(%)	2(%)	3(%)	4(%)	5(%)	M ± SD
1. I was curious about cadavers before I meet cadaver.	0.0	0.5	2.9	31.1	65.5	4.61 ± 0.57
2. I was interested in cadavers before I meet cadaver.	0.5	1.9	10.7	31.6	55.3	4.39 ± 0.79
3. I was excited about cadavers before I meet cadaver.	0.0	3.4	7.3	28.2	61.2	4.47 ± 0.78
4. I was anxious/fearful about cadavers before I meet cadaver.	18.9	42.2	17.0	16.5	5.3	2.47 ± 1.13
5. Before meeting a cadaver, there was a feeling of disgust towards cadavers.	32.5	44.7	14.1	7.3	1.5	2.05 ± 0.94
6. I was curious about the cadaver when I first meet cadaver.	0.5	3.4	7.8	38.3	50.0	4.34 ± 0.80
7. I was excited when I meet the cadaver for the first time.	0.0	8.3	9.2	40.8	41.7	4.16 ± 0.90
8. I felt fear/anxiety when I first meet a cadaver.	34.5	37.4	13.6	13.6	1.0	2.09 ± 1.05
9. The first time I meet a cadaver, I was disgusted.	40.3	36.9	12.1	10.2	0.5	1.94 ± 0.99
10. The cadaver should be more respected as it contributes to medical education.	1.5	1.0	5.8	26.7	65.0	4.53 ± 0.78
11. Photos/videos can be taken with the cadaver and the photos/videos can be shared on social media (facebook, instagram, twitter, snapchat etc.).	66.5	14.6	10.7	6.8	1.5	1.62 ± 1.01
12. Approaching the cadaver is as sensitive and important as approaching the patient.	0.0	1.5	2.9	29.6	66.0	4.60 ± 0.62
13. Gaining a sense of ethics and privacy regarding cadavers is important in terms of medical ethics and patient privacy.	0.0	1.0	1.9	22.8	74.3	4.70 ± 0.55
14. It is important to include cadaver dissection in the curriculum.	0.0	0.0	3.4	21.8	74.8	4.71 ± 0.52
15. Models or computer-assisted education can replace cadaver dissection.	38.8	33.0	11.7	5.8	10.7	2.17 ± 1.30
16. Active participation of students in cadaver dissection should be ensured.	0.5	0.5	2.9	29.1	67.0	4.62 ± 0.62
17. Hands-on dissection module sensitized me to my future professional life.	0.0	0.5	2.9	35.4	61.2	4.57 ± 0.58
18. Hands-on dissection module had the potential to broaden the range of learning outcomes required for future doctors.	0.0	0.0	3.9	37.4	58.7	4.55 ± 0.57
19. Hands-on dissection module supported the development of my psychomotor skills in preparation for clinical training.	0.0	1.0	7.8	33.5	57.8	4.48 ± 0.68
20. My participation in cadaver dissection provided me with more opportunities to develop professional skills than the demonstration of a prosectioned (previously dissected) cadaver.	0.0	1.0	7.3	36.9	54.9	4.46 ± 0.67
21. Hands-on dissection module informed me about the ethical values to be followed in dissection.	0.0	0.5	2.9	32.5	64.1	4.60 ± 0.57
22. From now on I will feel more responsible for using the tools and equipment of the dissection room and the school for effective learning.	0.0	0.0	1.5	35.4	63.1	4.62 ± 0.52
23. Hands-on dissection module increased my sense of gratitude towards people who donated their bodies to medical education.	0.0	0.5	1.5	26.7	71.4	4.69 ± 0.52
24. As a result of the hands-on dissection module, my interest and motivation towards medical education and the profession of medicine increased.	1.0	0.5	4.4	27.7	66.5	4.58 ± 0.69

Table 2. Comparative statistics between Group I and Group II

Questions	Group I (n=183) Mean ± SD	Group II (n=23) Mean ± SD	p
I was curious about cadavers before I meet cadaver.	4.65 ± 0.56	4.30 ± 0.55	0.001
I was interested in cadavers before I meet cadaver.	4.44 ± 0.77	3.95 ± 0.82	0.002
I was excited about cadavers before I meet cadaver.	4.52 ± 0.75	4.09 ± 0.90	0.007
The first time I meet a cadaver, I was disgusted.	1.87 ± 0.95	2.39 ± 1.15	0.032
Approaching the cadaver is as sensitive and important as approaching the patient.	4.63 ± 0.59	4.34 ± 0.77	0.045
Gaining a sense of ethics and privacy regarding cadavers is important in terms of medical ethics and patient privacy.	4.72 ± 0.55	4.52 ± 0.59	0.042
Hands-on dissection module sensitized me to my future professional life.	4.61 ± 0.57	4.26 ± 0.54	0.002
Hands-on dissection module had the potential to broaden the range of learning outcomes required for future doctors.	4.58 ± 0.55	4.26± 0.61	0.011
Hands-on dissection module supported the development of my psychomotor skills in preparation for clinical training.	4.54 ± 0.63	4.01 ± 0.85	0.001
From now on I will feel more responsible for using the tools and equipment of the dissection room and the school for effective learning.	4.64 ± 0.51	4.39 ± 0.58	0.032
As a result of the Hands-on dissection module, my interest and motivation towards medical education and the profession of medicine increased.	4.68 ± 0.53	3.78 ± 1.16	0.001

Gruop I- Those who study medicine with interest, Group II- those who study medicine with no interest

Cadaver dissection provides in-depth learning of the three-dimensional structure of the human body, realization of variations, adoption of task management and teamwork, experience of how best to hold the scalpel. [31-34]. The widespread use of computers has led technological applications to develop the idea that dissection rooms and cadavers are not necessary and useful today, but can be replaced by a well-equipped computer room. However, this developing trend can reach dangerous proportions when the idea of using technology oversteps the boundaries and claims to replace other practice-based procedures or elements [35]. The lack of adequate infrastructure and equipment for dissection rooms creates problems for educators and students. The time and cost constraints of cadaver dissection, the need for highly qualified teachers, the emotionally demanding nature of dissection, and the psychological distress it causes among students are seen as disadvantages. Therefore, reducing the use of cadaver dissection as an educational tool has a negative impact on anatomy knowledge. Conflicts of opinion between proponents of traditional anatomy education based on cadaver dissection and proponents of anatomy education based on technological applications can lead to disagreements [32,36]. Virtual simulation, which is a product of technology, reduces the dependence of education on cadavers as it provides an educational, efficient and effective training program [37]. However, cadaver dissection should not only be considered as a part of anatomy education but also in terms of socialization, acquisition of norms, values and ideologies of the profession, moral and ethical culture and emotional demands in the hidden curriculum of medical education [38].

As a result of the study conducted by Biswas and Bandyopadhyay in West Bengal, India in 2019, 82.2% of the participants agreed that it is important to include cadaver dissection in the curriculum, 85. 4% agreed that there should be a sense of respect for the dead body during cadaver dissection, 88.3% agreed that students should actively participate in cadaver dissections, but 79.6% of the participants did not agree with the idea that model and computer-aided education would replace cadaver dissection. In the form of agree or strongly agree, 96.6% of the volunteers who participated in our study stated that it is important to include cadaver dissection in the curriculum, 96.6% stated that the practical dissection module contributes to ethical values, 96.1% stated that they think that students should actively participate in cadaver dissection training, 71.8% stated that they think that models or computer-aided technological products cannot replace cadavers [39].

Darras et al. [40] evaluated the answers given by the participants with a 5-point scale in their study on virtual and cadaveric dissection laboratories enhanced in 2019. As a result of the study, they reported that the score of the response to the opinion that seeing radiographic anatomy on the virtual dissection table improves understanding was 4.08, and the score of the response to the opinion that the content seen on the virtual dissection table provides a better understanding of clinical cases as 4.09.

Souza et al. [41] conducted a study in a module on the values and ethical teaching of cadaver dissection in 2020. As a result of the study, the average of the answers to the survey questions on a 5-point scale was as follows: 3.75 for the opinion that the module develops empathy and emotions, 3.79 for the opinion that the dissection activity allows sharing ideas with others, 3.73 for the opinion that the module sensitizes students to their future professional life, and 3.97 for the opinion that the module develops respect for the cadaver. The mean and standard deviation values of the volunteers' answers to the question "Practical dissection module informed me about the ethical values to be followed in dissection" were 4.60 ± 0.57.

Izunya et al. [42] in 2010, 84% of the participants stated that cadaver dissection is the best method of learning anatomy, 39% stated that plastic models and computer-aided applications will not replace cadaver dissection in the future, 71% stated that cadaver dissection gives better results than prosected specimens and 90% stated that cadaver dissection is still very important and indispensable.

In a survey study conducted by Lalit et al. [43] in 2018 with ten newly admitted 150 first-year medical students, 90.57% of the participants stated that they thought that real hands-on training on cadaver dissection gave better results than showing cut specimens. 79.71% of the participants stated that they did not think that cadaver dissection technique would be replaced by plastic models etc. in the near future. 89.85% of the learners thought that cadaver dissection was indispensable in anatomy learning, 96.37% thought that cadaver dissection was the best method for learning anatomy, 95.65% thought that dissection was an important part of the medical curriculum in anatomy education.

As a result of our study, 91.8% of the participants agreed or strongly agreed with the question "My participation in cadaver dissection provided me with more opportunities to develop professional skills than the demonstration of a prosectioned (previously dissected) cadaver".

As a result of the cadaver dissection study conducted by Nikhil et al. [19] in 2020, 90.6% of the participants reported that the training they received helped them to have a good coping mechanism to overcome their ethical concerns. Regarding the educational value of cadavers in anatomy teaching, 71.9% of the learners participating in the same study rejected that other teaching materials such as videos and models can explain human anatomy better than cadavers.

As a result of the study conducted by Kolla et al. [44] in 2020, on the Perception of Virtual Reality Training Module for Anatomy Education by Medical Students, participants reported that virtual reality was a useful tool for learning the placement of anatomical structures and anatomical relationships in three dimensions. In fact, most of the participants stated that they would prefer anal reality to lectures and cadavers in learning anatomy. However, the authors expressed the opinion that even if virtual reality has benefits over lecture and cadaver, it will eliminate many important skills to be acquired through cadaver dissection and the psychosocial aspect of the cadaver.

As a result of the study conducted by Erer Kafa et al. [45] in 2021, 90.2% of the participants stated that sharing cadaveric images on social media is unethical, and 93.7% stated that gaining a sense of ethics and privacy about the cadaver is important in terms of medical ethics and patient privacy. It was determined that 81.1% of the students who participated in this study expressed a negative opinion by disagreeing or strongly disagreeing with the question "Photos/videos can be taken with the cadaver and the photos/videos can be shared on social media (facebook, instagram, twitter, snapchat etc.)."

As a result of the 5-point Likert (scaled 0-4) study conducted by Bahşi et al. [2] in 2021 investigating the emotional effects of cadaver on medical students before the student's first encounter with the cadaver, the mean answers of the participants to the questions "I am excited to encounter the cadaver" and "The idea of having an encounter with a cadaver is intriguing to me" were 2.36±1.16 and 2.75±1.01, respectively. In our study, the mean answers of the participants to the questions about their feelings before the first encounter with the cadaver were "I was curious about cadavers before I met cadaver, 4.61 ± 0.57; I was interested in cadavers before I meet cadaver, 4.39 ± 0.79; I was excited

about cadavers before I meet cadaver, 4.47 ± 0.78; I was anxious/ fearful about cadavers before I meet cadaver, 2.47 ± 1.13.

CONCLUSION

The importance of anatomy education in the medical curriculum and the importance of the cadaver in anatomy education has been emphasized for centuries. Although the applications related to learning the three-dimensional structure of anatomical structures offered to us by the developing technology contribute to learning anatomy, they cannot replace traditional cadaver dissection. Because cadaver dissection contributes not only to the acquisition of anatomy knowledge, but also to the preparation of future doctors for professional professional life with psychomotor, psychosocial and motivational aspects of being a physician. As a result of this study, the mean of the participant's answer to the question "Approaching the cadaver is as sensitive and important as approaching the patient" was 4.60 ± 0.62, the mean of their answer to the question "Gaining a sense of ethics and privacy regarding cadavers is important in terms of medical ethics and patient privacy" was 4.70 ± 0.55, the mean of their answer to the question "Models or computer-assisted education can replace cadaver dissection" was 2.17 ± 1. 30, "Practical dissection module sensitized me to my future professional life" was 4.57 ± 0.58, "Practical dissection module supported the development of my psychomotor skills in preparation for clinical training" was 4.48 ± 0.68, "As a result of the practical dissection module, my interest and motivation towards a medical education and the profession of medicine increased" was 4.58 ± 0.69 supports our hypothesis.

Although technology and artificial intelligence facilitate learning, the multifaceted benefits of the cadaver cannot be denied and the cadaver cannot be excluded from anatomy education. In fact, the role of the cadaver in medical education will be further strengthened by having the student personally dissect the cadaver rather than using previously dissected cadavers. In today's conditions, the importance of cadavers should be emphasized with similar studies against the increasingly difficult cadaver procurement due to the scarcity of cadaver donations and high costs, and cadaver procurement should be encouraged.

Advantages of the Study

* It has increased the sense of curiosity of students who are new to medical education to do cadaver dissection.
*It has increased the performance of the students after the distance education applied during Covid 19 and after the earthquake.
* It has increased students' interest in anatomy education.
* It has contributed to the gains of students about medical ethics.
* It has increased the students' motivation to become a physician.

Disadvantages of the study

* Insufficient number of cadavers.
* The module can be applied to a limited number of students.
* The application of the module in a limited time.

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Author Contributions: SB; Conception, Design, Materials, Data Collection, Analysis, Literature Review, Writing, Critical Review, Supervision.
DC; Conception, Design, Literature Review, Materials, Data Collection, Writing.
MD; Conception, Design, Literature Review, Critical Review, Supervision.

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Original Research

Evaluation of the Readability, Understandability, and Accuracy of Artificial Intelligence Chatbots in Terms of Biostatistics Literacy

İlkay Doğan[1,*], Pınar Günel[2], İhsan Berk[2], Buket İpek Berk[3]

[1] Department of Biostatistics, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
[2] Department of Biostatistics, Faculty of Medicine, SANKO University, Gaziantep, Türkiye
[3] Department of Biostatistics, Graduate Education Institute, SANKO University, Gaziantep, Türkiye

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Corresponding Author
İlkay Doğan, Assoc. Prof., PhD
Address: Gaziantep University, Faculty of Medicine, Department of Biostatistics, Gaziantep, Türkiye
E-mail: ilkay_dgn58@hotmail.com

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ABSTRACT

Objective: Chatbots have been frequently used in many different areas in recent years, such as diagnosis and imaging, treatment, patient follow-up and support, health promotion, customer service, sales, marketing, information and technical support. The aim of this study is to evaluate the readability, understandability, and accuracy of queries made by researchers in the field of health through artificial intelligence chatbots in biostatistics.

Methods: A total of 10 questions from the topics frequently asked by researchers in the field of health in basic biostatistics were determined by 4 experts. The determined questions were addressed to the artificial intelligence chatbots by one of the experts and the answers were recorded. In this study, free versions of most widely preferred ChatGPT4, Gemini and Copilot chatbots were used. The recorded answers were independently evaluated as "Correct", "Partially correct" and "Wrong" by three experts who blinded to which chatbot the answers belonged to. Then, these experts came together and examined the answers together and made the final evaluation by reaching a consensus on the levels of accuracy. The readability and understandability of the answers were evaluated with the Ateşman readability formula, Sönmez formula, Çetinkaya-Uzun readability formula and Bezirci-Yılmaz readability formulas.

Results: According to the answers given to the questions addressed to the artificial intelligence chatbots, it was determined that the answers were at the "difficult" level according to the Ateşman readability formula, "insufficient reading level" according to the Çetinkaya-Uzun readability formula, and "academic level" according to the Bezirci-Yılmaz readability formula. On the other hand, the Sönmez formula gave the result of "the text is understandable" for all chatbots. It was determined that there was no statistically significant difference (p=0.819) in terms of accuracy rates of the answers given by the artificial intelligence chatbots to the questions.

Conclusion: It was determined that although the chatbots tended to provide accurate information, the answers given were not readable, understandable and their accuracy levels were not high.

Keywords: Artificial Intelligence, Chatbots, Biostatistics Literacy, Readability, Understandability, Accuracy.

INTRODUCTION

Artificial intelligence (AI), which we have heard about frequently in recent years, is renewing itself day by day. Artificial intelligence can be defined as a technology of a computer or machine that has features such as learning, problem solving, decision making, and sometimes imitating human intelligence and thoughts. The basis of the concept of artificial intelligence is based on intelligent machines that first appeared with the question "Can machines think?" by Turing [1]. The term artificial intelligence was first used by McCarthy et al. [2] in 1955. Samuel [3] programmed the computer using two machine learning procedures, which provides learning how to play checkers. In addition to these, the historical development process of artificial intelligence can be examined in detail in the studies of Pirim [4], and Öztürk and Şahin [5]. Two events that can be considered as milestone for the concept and applications of artificial intelligence: artificial intelligence beating world chess champion Garry Kasparov in 1997, and in 2015, AlphaGo, an artificial intelligence developed by Google, beating a professional Go player without giving them an advantage. These successes of artificial intelligence have shown the potential of artificial neural networks and deep learning, and have enabled machine learning algorithms to find a place in everyday life [6]. Today, artificial intelligence is encountered in almost every field of science. It plays an active role in the early diagnosis and treatment of diseases, especially in the fields of medicine and health (radiology [7,8], oncology [9,10], cardiology [11,12], gastroenterology [13,14], ophthalmology [15,16], surgery [17,18], etc.).

Chatbots, a sub-branch of artificial intelligence, are products of the field of natural language processing (NLP). Chatbots are trained with various databases to answer questions posed to them by users [19]. Chatbots can understand, interpret, and answer users' questions via text or voice to simulate human-like conversation using natural language processing (NLP) [20]. In addition, chatbots can answer consecutive questions, accept errors in their answers and correct themselves with reinforcement learning, understand and answer different languages, and refuse to answer inappropriate questions [19]. Chatbots are constantly improving themselves with the machine learning algorithms in their background to provide correct answers and perform better. The most preferred chatbots by users are ChatGPT (OpenAI), Copilot (Microsoft), Gemini (Google) due to their free versions and easy accessibility.

Main Points

- Although chatbots tend to provide accurate information, the results showed they were not readable, understandable, and had low accuracy levels.
- One of the most important limitations of chatbots is the lack of evidence-based information sources. Therefore, it is very important to check their answers.

Chatbots have been frequently used in many different areas in recent years, such as diagnosis and imaging, treatment, patient follow-up and support, health promotion, customer service, sales, marketing, information and technical support [21-26]. Despite this, there are still many question marks on the responses given by chatbots, and researchers are evaluating the readability, understandability and accuracy of the responses given by chatbots [20, 27-32]. In this study, the responses given by chatbots are evaluated for the first time in terms of biostatistical literacy. The aim of this study is to evaluate the readability, understandability, and accuracy of queries made by researchers in the field of health through artificial intelligence chatbots in biostatistics. In this context, it is thought that the results obtained will be guiding in the use of chatbots, especially in the field of health sciences.

MATERIALS AND METHODS

A total of 10 questions from topics that are thought to be frequently questioned by researchers in the field of health in basic biostatistics (deciding on appropriate statistical tests, interpretation of the results of applied tests, some basic statistical definitions, sample size calculation-power analysis, etc.) were determined by 4 experts (Table 1). The determined questions were addressed to artificial intelligence chatbots by one of the experts and the answers were recorded. In this study, free versions of most widely preferred ChatGPT4, Gemini and Copilot chatbots were used. The recorded answers were independently evaluated as "Correct", "Partially correct" and "Wrong" by three experts who blinded to which chatbot the answers belonged to. Then, these experts came together and examined the answers together and made the final evaluation by reaching a consensus on the accuracy of the answers. In addition, the readability and understandability of the answers were assessed by using the Ateşman readability formula,

Sönmez formula, Çetinkaya-Uzun readability formula and Bezirci-Yılmaz readability formulas.

Ateşman Readability Formula

The Ateşman readability formula was proposed by Ateşman in 1997 to assess the readability of Turkish texts. This measure is an adaptation of the formula proposed by Flesch in 1948. Emphasizing the difference in average word and sentence lengths between English and Turkish, Ateşman adapted the variables of the Flesch formula to Turkish sentence and word lengths and created his own formula [33].

$$\text{Readability score} = 198.825 - 40.175(x1) - 2.610(x2)$$

$$x1 = \frac{\text{(Syllable count)}}{\text{(Word count)}}$$

$$x2 = \frac{\text{(Word count)}}{\text{(Number of sentences)}}$$

According to the Ateşman readability formula, readability levels are scored as "1-29: very difficult", "30-49: difficult", "50-69: medium difficulty", "70-89: easy", "90-100: very easy" [33].

Sönmez Formula

In his study, Sönmez (2003) found that the Fog index used to evaluate the understandability of texts gave invalid results on Turkish texts and stated that the prerequisite for the understandability of a text is to know the meaning of the words. In this context, he created a formula based on unknown words for Turkish [33].

$$\text{Word rate} = \frac{\text{Number of words in the text}}{\text{Number of sentences in the text}}$$

$$\text{Difficulty ratio} = \frac{\text{Number of foreign words, idioms, terms concepts, methaphors, smiles, symbols, formulas in the text}}{\text{Number of words in the text}}$$

$$\text{Meaning ratio} = \frac{\text{Number of foreign words, idioms, terms concepts, methaphors, smiles, symbols, formulas in the text}}{\text{Number of sentences in the text}}$$

$$\text{Understandability rate} = \frac{\text{Meaning ratio}}{\text{Word rate}} \times \text{Difficulty ratio}$$

According to the Sönmez formula, the understandability rates and understandability levels are as follows: "0-0.00001: full communication is achieved", "0.00099-0.0001: text is clear and understandable", "0.03-0.001: text is understandable", "0.08-0.04: text can be understood with help", "0.15-0.09: text is difficult to understand", "0.25-0.16: text is blurry", "0.98-0.26: text is meaningless", "1.00-0.99: text is completely meaningless" [33].

Çetinkaya-Uzun Readability Formula

This formula was proposed by Çetinkaya [34] and is used to define and classify the readability levels of Turkish texts.

$$\text{Readability score (RS)} = 118.823 - (25.987 \times \text{AWL}) - (0.971 \times \text{ASL})$$

$$\text{Average Sentence Length (ASL)} = \frac{\text{Total number of words}}{\text{Total number of sentences}}$$

$$\text{Average Word Length (AWL)} = \frac{\text{Total number of syllables}}{\text{Total number of words}}$$

According to the Çetinkaya formula, readability levels are classified as "0-34: inadequate reading level", "35-50: educational reading level", "51+: independent reading level" [34].

Bezirci-Yılmaz Readability Formula

It is another formula proposed to define and classify the readability levels of Turkish texts [35]. Bezirci-Yılmaz formula has more detailed variables than the previous formulas. While the average word length is directly included in the equation in Ateşman and Çetinkaya-Uzun formulas, in Bezirci-Yılmaz formula, words are included in the equation separately according to the number of syllables.

$$\text{New Readability Value (NRV)} = \sqrt{(\text{AWS} \times [(H3 \times 0.84) + (H4 \times 1.5) + (H5 \times 3.5) + (H6 \times 26.35)])}$$

$$\text{Average number of words in a sentence (AWS)} = \frac{\text{Number of words in the text}}{\text{Number of sentences}}$$

$$H3 = \frac{\text{Number of three-syllable words in the text}}{\text{Total number of sentences}}$$

$$H4 = \frac{\text{Number of four-syllable words in the text}}{\text{Total number of sentences}}$$

$$H5 = \frac{\text{Number of five-syllable words in the text}}{\text{Total number of sentences}}$$

$$H6 = \frac{\text{Number of words with six or more syllables in the text}}{\text{Total number of sentences}}$$

According to the Bezirci-Yılmaz formula, readability levels are evaluated as "1-8: primary school", "9-12: high school", "13-16: undergraduate", "16+: academic" [35].

Statistical Analysis

Descriptive statistics of the data obtained from the study are given as mean±standard deviation or median (Q1-Q3) for quantitative variables and percentage values for categorical variables. One-Way Analysis of Variance (ANOVA) and Kruskal Wallis test with Dunn's posthoc test were used to compare the Ateşman Readability Formula, Sönmez Formula, Çetinkaya-Uzun Readability Formula and Bezirci-Yılmaz Readability Formula scores of the chatbots. The Fisher-Freeman-Halton test was used to compare the accuracy rates of the chatbots. In evaluating the accuracy rates of the answers recorded for each chatbot, the agreement between the experts was evaluated with the Kendall concordance coefficient. The Kendall concordance coefficient measures the amount of agreement between the decisions of K experts, each measured with an ordinal scale for N items [36]. The analyses were performed with IBM SPSS Statistics 23.0 program. $p<0.05$ was considered statistically significant.

Table 1. Questions Addressed to Chatbots

1.	In a city, the vitamin D levels in the blood of 35 women living in rural areas and 35 women living in urban areas were examined. It is known that the vitamin D levels in both groups follow a normal distribution. Which significance test should be used to evaluate whether there is a difference between these two regions in terms of the women's vitamin D levels?
2.	The hemoglobin levels of twenty anemic patients are measured before and one month after receiving an iron supplement. It is known that the hemoglobin levels do not follow a normal distribution in both measurements. Which significance test should be used to evaluate whether there is a difference in hemoglobin levels between the two measurements?
3.	The correlation coefficient between the ages and systolic blood pressures of a group of individuals is found to be $r = 0.80$ ($p<0.001$). Given that the variables follow a normal distribution, how is the relationship between these two variables interpreted?
4.	What does the normal distribution of data mean in significance tests? What are the most commonly used tests to evaluate the normal distribution of data?
5.	Can you interpret the given analysis outputs statistically? (IBM SPSS Statistics 23 output)
6.	According to the results of a previous similar study, the average of experimental group was found to be 25±2.3, while the average of control group was found to be 20±1.8. Can you calculate the minimum sample size required for the experimental and control groups in a study to be conducted on a similar topic ($\alpha=0.05$; $\beta=0.80$)?
7.	In a study, 15 out of 30 patients with headaches are given Drug A and 15 are given Drug B. The time taken for the drugs to relieve the pain is recorded. It is desired to assess whether there is a difference between Drug A and Drug B in terms of time taken to relieve pain. What is the hypothesis of such a study?
8.	When data do not follow a normal distribution, which measures of central tendency and dispersion should be used?
9.	Can you interpret the name and output of the given graph statistically? (IBM SPSS Statistics 23 output)
10.	Can you explain the concepts of "variable" and "parameter" in statistics?

RESULTS

The Ateşman readability formula average scores of the responses given to the questions specified in Table 2 of ChatGPT4, Gemini and Copilot chatbots were 42.88±7.77, 43.28±6.05 and 49.46±13.4, respectively. As a result of the Ateşman readability formula, it was concluded that the readability levels of all chatbots were "difficult". The understandability rates obtained from the Sönmez formula for the responses received from ChatGPT4, Gemini and Copilot chatbots were calculated as 0.003±0.003; 0.002±0.002 and 0.006±0.009, respectively, and "text is understandable" for all chatbots. Similarly, the Çetinkaya-Uzun readability formula averages of the responses given by ChatGPT4, Gemini and Copilot chatbots were calculated as 30.16±4.51, 29.39±3.74 and 33.77±7.71, respectively and "insufficient reading level" was found for all chatbots. Finally, the Bezirci-Yılmaz readability formula averages of the responses received from ChatGPT4, Gemini and Copilot chatbots were calculated as 47.0±22.92; 93.55±12.56 and 46.92±10.72, respectively, and it was concluded that the Bezirci-Yılmaz readability level for all chatbots was at the "academic level".

When artificial intelligence chatbots were compared in terms of readability and understandability measures, only Gemini chatbot ($p<0,001$ vs ChatGPT 4 and $p<0,001$ vs Copilot) showed a statistical difference from ChatGPT4 and Copilot chatbots in terms of Bezirci-Yılmaz readability level (Table 2).

No statistically significant difference was obtained in terms of correct answer rates of the artificial intelligence chatbots ($p=0.819$) (Table 3). The accuracy rates of ChatGPT4, Gemini and Copilot chatbots were found to be 60%, 60% and 80%, respectively. Also, the Kendall concordance coefficients of agreement between the experts for ChatGPT4, Gemini and Copilot chatbots were found 66%, 83,1% and 85,4%, respectively.

Table 2. Comparison of readability and understandability measures in chatbots

Readability and Comprehensibility Criteria	Chatbots	Mean±SD	Median (Q1-Q3)	p		
Ateşman Readability Formula	ChatGPT 4 (A)	42.88±7.77	42.93 (37.95-47.46)	0.266 Ψ		
	Gemini (B)	43.28±6.05	44.14 (37.97-45.86)			
	Copilot (C)	49.46±13.4	48.51 (42.64-55.16)			
Sönmez Formula	ChatGPT 4 (A)	0.0032±0.0032	0.0031 (0.0005-0.0049)	0.401¥		
	Gemini (B)	0.0023±0.0025	0.0019 (0.0002-0.0032)			
	Copilot (C)	0.0062±0.0086	0.0036 (0.0006-0.0071)			
Çetinkaya-Uzun Readability Formula	ChatGPT 4 (A)	30.16±4.51	31.33 (26.52-32.54)	0.194 Ψ		
	Gemini (B)	29.39±3.74	29.51 (26.28-32.65)			
	Copilot (C)	33.77±7.71	33.21 (26.48-37.25)			
Bezirci-Yılmaz Readability Formula	ChatGPT 4 (A)	47±22.92	42.78 (26.09-74.36)	**<0.001*¥ B>A=C**	ChatGPT 4 - Copilot	**0,859**
	Gemini (B)	93.55±12.56	96.37 (88.28-100.19)		ChatGPT 4 - Gemini	**<0,001***
	Copilot (C)	46.92±10.72	44.73 (39.91-53.46)		Copilot- Gemini	**<0,001***

*p<0.05; Ψ: One-way ANOVA; ¥: Kruskal Wallis test (Dunns' posthoc test); SD: Standard Deviation; Q1: 1st Quartile; Q3: 3rd Quartile

Table 3. Comparison of accuracy rates of chatbots in line with expert opinions

Variables n (%)		False n (%)	Partially True n (%)	True n (%)	p
Group	Chat GPT	1 (10)	3 (30)	6 (60)	0.819
	Gemini	2 (20)	2 (20)	6 (60)	
	Copilot	1 (10)	1 (10)	8 (80)	

The Fisher-Freeman-Halton test

DISCUSSION

According to the answers given to the questions addressed to the artificial intelligence chatbots, it was concluded that the score levels obtained from the Ateşman readability formula were "difficult". Similarly, it was determined that the score levels obtained from the Çetinkaya-Uzun readability formula were "insufficient reading level". The readability levels of the answers being "difficult" or "insufficient reading level" can be interpreted as the biostatistics literacy levels of the researchers using the chatbots should be high. Because the use of expressions and terms specific to the field of science reduces the readability levels of the answers. This shows that the researchers using the chatbots should have sufficient knowledge of field-specific expressions and terms. It was determined that the score levels obtained from the Bezirci-Yılmaz readability formula were "academic" level. Therefore, it can be said that in order for the answers given by the chatbots to be readable, the users should have an academic level of education specific to that field. It was also determined that the accuracy rates of the chatbots were not sufficient.

There are many studies evaluating the readability, understandability, and accuracy of artificial intelligence chatbots in different fields of health sciences with similar results to our study [28, 31, 32, 37-43]. Hancı et al. [28] examined ChatGPT, Bard, Gemini, Copilot, Perplexity chatbots using ARI (Automated Readability Index), FKG (Flesch-Kincaid Grade), and FRE (Flesch Reading Ease) indexes to evaluate the readability, reliability, and quality of responses related to palliative care. It was concluded that the quality and readability of the responses were not sufficient and that the responses provided by the chatbots were at the 6th grade reading level. Hershenhouse et al. [31] evaluated ChatGPT using Flesch-Kincaid Reading Ease (FRE), Flesch-Kincaid Grade Level (FKG), and Automated Readability Index (ARI) in their study to evaluate the level of prostate cancer knowledge and concluded that accuracy and understandability was low, and texts are readable. Önder et al. [32] evaluated ChatGPT 4.0 using FRE and FKG to evaluate the reliability and readability of responses related to hypothyroidism in pregnancy, and as a result of the FRE score, it was found that the text was difficult to read, and the level of education required to understand the responses was university level. Güven et al. [37] evaluated the performance of ChatGPT 3.5, ChatGPT 4.0 and Google Gemini artificial intelligence chatbots using FRE and FKG measures in responding to patient questions about dental injuries as a result of trauma and concluded that readability was difficult, and the level of education required university level reading skills. In the study conducted by Gajjar et al. [38], ChatGPT 3.0, ChatGPT 3.5 and ChatGPT 4.0 were evaluated using FRE and FKG measures to assess the accuracy of responses given to patients' questions for neurosurgical procedures. The study found that the readability level was difficult, and the education level was at a postgraduate level. In the study conducted by Ayo-Ajibola et al. [39], ChatGPT was evaluated using FRE and FKG measures on tracheostomy care recommendations. The readability of the answers to the questions corresponding to the low education level was found to be easy, the readability of the self-care questioning category was found to be difficult, and the readability levels for all questioning categories, except for the special situation questioning, were found to be at the 12th grade level or above. In the study conducted by Gondode et al. [40], they compared the accuracy of patient education tools for chronic pain medications created by ChatGPT with materials from traditional sources. Readability was evaluated using FRE and FKG measures. They concluded that traditional sources are more readable and potentially easier to understand. Steimetz et al. [41] examined Google Bard, ChatGPT using FRE and FKG to evaluate the ability to accurately explain pathology reports to patients and suggested that artificial intelligence chatbots can simplify pathology reports for patients and identify key details important for patient management, however, they concluded that interpretations should be used with caution as they are not perfect and that fact-checking solutions should be developed before integrating these tools into the healthcare environment. Carlson et al. [42] examined ChatGPT, Google Bard, Microsoft Bing, Perplexity, Claude using FRE and FKG to evaluate the accuracy and readability of responses to questions about vasectomy and concluded that all five artificial intelligence chatbots had an average FRE score below 50 and above a 10th grade reading level. They suggested that artificial intelligence chatbots may perform similarly in terms of their accuracy but may differ in terms of ease of understanding by the general public. Pradhan et al. [43] evaluated ChatGPT, DocsGPT, Google Bard, and Bing Chat using FRE and FKG to compare human-based patient education materials on cirrhosis, and concluded that the readability level was readable by someone with an 8th grade education level and understandable, but recommended that further work be done to easily accepted artificial intelligence chatbots in routine clinical practice.

Limitations and Strengths

In this study, parallel results were obtained with the results of similar studies. The limitation of the study can be stated as the small number of questions addressed to artificial intelligence chatbots. While indexes developed for foreign languages were used in previous studies evaluating Turkish responses in chatbots, the use of indexes adapted to Turkish in this study can be considered as a strength of the study. In addition, it is thought that being the first research in the field of biostatistics will contribute to the literature by providing an important perspective.

CONCLUSIONS

Recent studies have shown that the results of artificial intelligence chatbots are not readable, understandable, and have low accuracy levels. Although chatbots tend to provide accurate information, they have limitations available. One of the limitations of chatbots is the lack of evidence-based information sources. It can be difficult to know whether the information is reliable because it is not clear whether it is obtained from a valid source [28].

Although artificial intelligence chatbots are practical in terms of fast access to information and ease of use today, their readability, understandability and accuracy are not sufficient in areas that require expertise, such as biostatistics. Therefore, considering that biostatistics is an integral part of medical and health sciences research, researchers need to have a high level of knowledge, experience and academic reading level specific to the field of biostatistics. Although access to artificial intelligence chatbots is thought to be fast, easy and practical, it is seen that the information obtained from chatbots is not completely accurate and the information they provide is insufficient. As a result, it is considered appropriate that chatbots cannot be used to contribute to science, but only as a tool on the way to knowledge.

“To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of.” (R. A. Fischer, 1930).

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Original Research

Abu Bakr Muhammad al-Razi's, a Distinguished Physician in Point of Knowledge and Experience, About the Cases That Happened to Him

Nuray Yaşar Soydan[1, *], Ahmet Acıduman[2], Çağatay Aşkit[3], Berna Arda[4]

[1] Fevzi Çakmak Family Health Center, Kayseri, Türkiye
[2] History of Medicine and Ethics Department, Ankara University Faculty of Medicine, Ankara, Türkiye
[3] Department of Ancient Languages and Cultures, Sub-Department of Latin Language and Literature, Ankara University, Faculty of Languages, History and Geography,Ankara, Türkiye
[4] History of Medicine and Ethics Department, Ankara University Faculty of Medicine, Ankara, Türkiye

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Corresponding Author
Nuray Yaşar Soydan, MD
Address: Fevzi Çakmak Family Health Center, Kocasinan, Kayseri, Turkiye
E-mail: nuray51yasar@gmail.com

ABSTRACT

Objective: The aim of this study is to show the medical experience and practices in the third chapter of titled "About the Cases that Happened to Razi" of the book titled The Knowledge and Experience of the Distinguished Physician's in the Book of Aphorisms or The Secrets of Medicine of Abu Bakr Muhammad Razi Interpreted by Gerard of Cremona From Toledo.

Methods: The relevant section was translated from Western Medieval Latin into Turkish. Then translated into English on the basis of the Turkish text. In the light of the data obtained, Razi's approaches to case narratives were evaluated with the approaches of his predecessors, Hippocrates and Galen, and the case narratives in his own works. During the discussion, basic sources of medical history, the works of his predecessors Hippocrates and Galen, Razi's own works and modern sources have been used.

Results: As a result of the evaluation, in the cases narrated by Razi, there are people from different social groups such as Razi himself, the ruler, his friend and the slave. Findings such as the diseases that caused the case narratives, the treatment methods applied for these diseases, the presence of a negative opinion towards the physician, the feeling of trust between the physician and the patient, instant clinical observations and the duration of treatment have been obtained.

Conclusion: In Razi's case narratives, it has seen that he was influenced by the theoretical knowledge and practices of his predecessors, Hippocrates and Galen. In the case narratives presented by Razi, it has been noticed that while the patient group consisted of different people, some cases based on complaints such as paralysis, swelling, heat stroke, discharge, stomach pain and burning were repeated. In these narratives, it can be said that Razi's style is dominated by clarity, comprehensibility and simplicity.

Keywords: Razi, Aphorisms, Case Narratives, History of Medicine

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INTRODUCTION

The word case comes from the Latin word "casus, us, m" meaning "fall, fall, situation, case, and event" [1]. Nissen and Wynn [2] included the following definition made by Taber regarding the definition of the case in their study: "A formal summary of the current symptoms, diagnostic studies, treatment process and outcome of a single patient and his/her disease." Nutton [3] has stated that medicine has been partly a public art since the time of Hippocrates and that the physician has to persuade his patients and observers with words as well as actions. Millan [4] has emphasized that case narratives provide examples of transforming theoretical knowledge into practice, improve observation skills, provide the physician with competence in medical learning and healing skills, and improve the physician's literary side. Narratives are not only the primary forms of communication used to convey information, but also provide an opportunity to organize experience, thought, and action. Narratives describe an event, setting, or situation and its causal and temporal order, along with its origins in the past and impressions of what might happen in the future [5].

When we look at the first examples of case narratives, the Edwin Smith Papyrus, which belongs to the 16th and 17th dynasties in Ancient Egypt and dates back to approximately 1600 BC, comes to mind. In these papyri, each case has a title and is usually written in red ink. The title means "application, practical medical practice and experience" and refers to knowledge gained from practical experience. These texts contain forty-eight case narratives discussing head and upper body injuries or disorders. These are not individual case histories, but typical cases [6].

Main Points

- The translation of this medical text is based on the 1544 Basel edition of the book. The relevant section has been first translated first from Latin into Turkish and then from Turkish into English.
- The cases described are important in terms of reflecting Razi's clinical experience and power of observation.
- While Razi was structuring this work, it was noticed that he was influenced not only by the works of his predecessors Hippocrates and Galenus, but also by his own works.
- This study is considered to be a primary source for studies to be carried out in the field of History of Medicine.

The richest source of case narratives is his work called *De Morbis Popularibus*/*Epidemics* which is included in the *Hippocrates Corpus* and consists of seven books. In this work of Hippocrates, there are approximately more than 100 case narratives [7]. These case narratives of Hippocrates contain very little patient presentation and are based on the experiences of travelling physicians describing the assessment of patients. In the case narratives, which are literary, historical and nosological fragments, the anamnesis have been remaind secondary [8]. In most cases, only the patient's name, occupation, and place of residence are given, while women and children are listed according to the relative's affiliation. Description of the patient's condition begins at the onset of the illness or possibly on the day the patient is visited. A key feature of these cases is the careful day-by-day recording of symptoms. In addition to the psychological problems that cause the diseases and the patient's careless lifestyle, poor nutrition or bad habits such as drunkenness and sexual indulgence, causes such as brain fever, dysentery, childbirth, puerperium, gynecological disease, swelling in the ear, high fever, nose bleeding have also been recorded. In these cases, where the treatment method is rarely described and the author is an anonymous observer, the patients are described according to gender, age, lifestyle and represent people from all walks of life, including rich and poor, women and pregnant women, young girls, young men, slaves and visitors from abroad [4,9].

Another physician who contributed to the case narratives was Galen. *Galeni de Praecognitione*/*On Prognosis*, *De Usu Partium*/*The Usefulness of the Parts of the Body* and *Methodus Medendi*/*Method of Healing* have rich case examples [4]. Nutton [3] reported that Galen was interested in Greek literary classics and that there were sophists and orators among his friends. Thus, he stated that Galen used a range of literary and rhetorical skills and was able to change the tone, style and tempo of his narratives according to the situation and to avoid monotony. It is possible to see Nutton's comments on Galen' rhetoric skills in Galen's work *Galeni De Praecognitione* [10]. When this work of Galen was examined, it has been determined that there were fascinating case narratives. The case narratives he put forward include the following findings regarding patient groups and cases: As a result of a young man contracting an acute illness at the beginning of autumn, it was determined that Galen performed fever monitoring, pulse and urine examination. In this case, it has been stated that while there was no treatment planning,

only medication was administered. Another case described is that of a woman. It has been determined that there was no physical illness in the woman, but a psychological disorder arising from sadness and love has been mentioned. Galen also touched upon the psychological discomfort experienced by a slave due to anxiety and fear. It is noteworthy that medical advice was not included in these cases. It has also been observed that Boethus' son's diet was regulated, showing that Galen was also the physician of his family members and cases showing that Boethus' wife suffered from discharge were also included. Galen reported that in the treatment of discharge, he discharged aqueous humor from the woman, took some Indian hyacinth oil and rubbed the woman's stomach, kept her feet and hands warm, and applied scented substances to her nose [10]. Boethus appears as the patient's relative in these cases. It has been observed that in these cases, priority is given to predictions to determine the diagnosis rather than treatment.

The concept of case used by medieval Islamic scholars as Arabic Tecarib and Mücerrebat, like the medical theories put forward by Greco-Roman scientists, rhetorical and didactic methods also found a place in Islamic civilisation, and it was soon observed that Islamic medical writers began to use these narrative patterns in their own works [4]. One of the physicians who used these narrative patterns is Razi. Physician-philosopher Razi (865-925), known in the West as "Rhazes, Rasis, Albubator, Abubertus, Abubater, Bubikir, Abubeter" was born in the city of Ray in Khorasan [11,12]. According to Browne [13] Razi was involved in music and played the oud in his youth. He also worked as an alchemist in his youth and focused on medicine in the following years [14]. Regarding the process of Razi' beginning medical education, Aşkit [15] states in his study after studying Greek science, he left the city of Ray in his 30s and started to study medicine in Baghdad, and after staying there for a while, he returned to Ray and was appointed as the chief physician at the Rey Hospital, where he served patients with his students and their students, diagnosing difficult cases. And also he has reported that he practiced a clinical system that reached from his students to himself. His blindness due to cataract towards the end of his life, al-Biruni attributed it to his exposure to toxic fumes [16] and dazzling light in his chemistry laboratory on the other hand, Browne [13] has stated that he did not agree to have the operation. There are different information in the sources about the date of his death, and the general acceptance is that he was 60 years old in Ray on October 27, 925 [17].

Razi' clinical explanations, consist of his medical experiences, professional assistant notes, treatment-related narratives and case notes [4]. Razi described the cases in detail in his writings as an educational tool and as a document of the various diseases he diagnosed and treated [18]. Razi' works *Liber Continens*, *Kitabü't-Tecarib* and *Kitāb Sirr ṣināʿat al-ṭibb* which are voluminous in terms of case narratives, are known. His work titled *Liber Continens* is a very well-equipped work in terms of presenting his own case narratives. Within *Liber Continens*, there is a group of 33 clinical cases discovered by E.G. Browne. These were later edited by Meyerhof and translated into English [19]. It is known that Razi structured work called *Liber Continens* is based on Hippocrates' *De Morbis Popularibus* and *Galen's In Hippocratis Epidemias Commentaria*/*Hippocrates's Comments on Epidemic Diseases*, *Hunayn's Comments on Galen*, and *Hunayn's Questions and Summaries of the Epidemic in the Form of Answers*, *Hunayn's Sayings from Epidemics* and *Questions Concerning Urine from Epidemics* [20,21]. According to Meyerhof [21] there are case narratives on internal diseases, fevers, eye and gynecological diseases in *Liber Continens*. Other information provided by Meyerhof [21] includes that the patient group consisted of people from different professions, that Razi tried to cure each person by examining them regardless of their economic and socio-cultural level, and that he applied treatment based on the cause by revealing the clinical status of the patients. Moreover, it has been noticed that Razi tried to diagnose gynecological diseases and arranged treatment, but Razi was forced to make a diagnosis based on the information given by his wife (case fifteen) or midwife (case twenty-six) without personally seeing the female patient.

Razi's other work in which he included case narratives is *Kitāb Sirr ṣināʿat al-ṭibb*, which also forms the source of this study. This book is a study about the professional secret of the physician. It is also known as *Maqāla fī Sirr Ṣināʿa al-Ṭibb* or *Asrār Funūn al-Ṭibb* [22]. The Arabic text of this book consists of five books. The original Latin text of the book is consists of six chapters. This book, also known as aphorisms, was used as vademecum for a long time [12]. Rosa Kuhne published this study in 1982 in "El Sirr Sina'at al-Tıbb de Abu Bakr Muhammad b. Zakariyya' al-Razi" [23] in 1984, "Abu Bakr Muhammad b. Zakariyya' al-Razi: Traduccion" [24] and in 1985, "Abu Bakr Muhammad b. Zakariyya' al-Razi III" [25] published three articles in Estudio with Arabic, Latin and Spanish translations. These articles were published in Al-Qantara: Revista de Estudios Arabes (Journal of Arab Studies) issues 3(1), 5(1) and 6(1) respectively. Under

the title *Aphorismi Rasis,* this work was published in Milan in 1481, in Venice in 1494, 1497, 1500, 1508, in Lyon in 1511, and in Basel in 1544 forming part of the *Opera Exquisitiora* [25]. The book translated into Spanish by Rosa Kuhne also consists of six chapters.

Case narratives are a visual and linguistic method of making an assessment of the patient's medical or social history, clinical symptoms, course of disease, methods used, disease relationships and side effects [2]. Case narration helps the physician to interpret the symptoms observed in the patient, transforms the physicians power of observation into intelligible expression, provides effective communication by actively listening to the patient, develops a sense of trust between the physician and patient through effective communication, and strengthens the physicians narrative skills [26]. To be precise, the case narrative is an important part of the medical experience, allowing the physician to know what he has done to the patient before, facilitating the continuation of the patient's treatment, and ensuring the continuity of medical history [27]. As seen in this study, it is also important for the physician to provide information about his own life and disease. In both theoretical and practical aspects of medical education, we must always keep in mind the famous Latin proverb "verba volant, scripta manent".

MATERIALS AND METHODS

In this study has been used the book titled *The Knowledge and Experience of the Distinguished Physician's in the Book of Aphorisms or the Secrets of Medicine of Abu Bakr Muhammad Razi Interpreted by Gerard of Cremona From Toledo* which is situated in pages 517-546 of his book titled *Abubetri Rhazae Maomethi, ob usum experientiamque multiplicem, et ob certissimas ex demostrationibus logicis indicationes, ad omnes praeter naturam affectus, atque etiam propter remediorum uberrimam materiam, summi medici opera exquisitiora, quibus nihil utilius ad actus practicos extat, omnia enim penitus quae habet aut obscuriora, aut Galenus fusiora, fidellissime doctissimeque exponit, & in lucem profert* [28] of which contains the works of Abu Bakr Muhammad Zakariyya al-Razi's translated into Latin. The chapters in *Abubetri Rhazae Maomethi Scientia Peritiaque Insignis Medici in Libros Aphorismorum, sive Secretorum Medicinalium Gerardo Toletano Cremonensi Interprete* are:

1) About the Prognostication of Future Events
2) About Experiences and Trust
3) About the Cases That Happened to Razi
4) About Diets, Treatments and Foods
5) About the Words of Hippocrates
6) About Sciences and Thinking Ability, Without These There can be no Honest Physician

Study, has been carried out on the the book of *About the Incidents That Happened to Abu Bakr Muhammad Razi', a Distinguished Physician in Terms of Knowledge and Experience, the Third Book of Aphorisms*. Firstly, based on the 1544 Basel edition of the mentioned work, the relevant section was translated from Western Medieval Latin into Turkish. Then translated into English on the basis of the Turkish text. The following dictionaries have been used in the translation of the Latin text: Charlton T. Lewis (1997) *An Elementary Latin Dictionary* [29], J.F Niermeyer (1933) *Medieval Latin-French (English) Dictionary* [30], and *Oxford Latin Dictionary* (1968) [31], and DMLBS [32]. = R. K. Ashdowne, D. R. Howlett, & R. E. Latham (eds.). Dictionary of Medieval Latin from British Sources. Oxford: British Academy. https://logeion.uchicago.edu. For the Greek dictionary Liddell and Scott (1889) *An Intermediate Greek-English Lexicon* [33], for English words and translations https://www.seslisozluk.net [34] have been consulted. Apart from these, there are Redhouse JW' (1996) *Turkish-English Lexicon* [35] and Steingass F (2005) *Persian-English Dictionary* [36] and Güneş (2011) *Arapça-Türkçe Sözlük* [37]. In determining the Turkish equivalents of plant and animal names, measurement units, and medical terms in the Latin text, the study that Aşkit (2019) translated into Turkish with the name "Razi: Practica Puerorum" has been also used [15].

In the light of the data obtained, Razi's approaches to case narratives were evaluated with the approaches of his predecessors, Hippocrates and Galen, and the case narratives in his own works. During the discussion, basic sources of medical history, the works of Hippocrates and Galen, Razi's own works and modern sources have been used.

The ancient medical books mentioned in the text are written in Latin-English order at the first mention, and then the Latin title of the book is used. The Arabic book names included in the study are written by Prof. Dr. Ahmet Acıduman. The original Latin text is presented in annex-1 at the end of the study.

RESULTS

There have been 21 case narratives in total. Among the

patient groups that Rhazes describes, firstly he is himself, then the king, his friend, slaves and citizens. It is noteworthy that among the diseases he deals with, there are cases caused by psychological disorders and the patient's careless lifestyle, paralysis, drunkenness, fever, stomach ache, and swelling in the ear. Below you will read the narratives that Razi experienced.

1) During the time I was studying philosophy and medicine, I had many sleepless nights; I lost sleep; I did things that were not effective; I couldn't find anything more beneficial than lotus oil; by snorting it, I let the air out; I was eating cooked and raw lettuce. However, I had difficulty seeing and lacked sexual desire. I could not find anything more useful to me than eating from sparrows, eggs, and their own juice, blackbirds, and prepared in cinnamon and pepper chickens, and pigeons. My strength and memory are restored in the best way.

2) I made oil for this, there is nothing better than this: A piece of each of pine seed oil, banyan oil, wallflower oil, sweet apple oil, the middle part of the gall of sparrows when they feel sexual desire, and a muskal of the yellow wallflower seed should be taken. All of them should be boiled over low heat. After taking it off the heat, half muskal musk should be mixed into it. After bathing, the genital area and chest are lubricated with it, it gathers strength and increases desire.

3) Another case happened to me in the city of Zelergebani; A man came to me with complaints of fear and heart trembling for no reason. Frankly, among the medicines, I could not find anything that was as beneficial as falcon meat cooked in sweet marjoram juice and thin white wine. I anointed his body with fragrant oils, and he was fully restored to health.

4) Another unexpected case; the feeble old people, the ethicists, and those deprived of health do not know the cure. This treatment benefits them more than eating birds, doves, chickens, pigeons and sparrows cooked in fragrant wine and drinking fresh wine.

5) Another unexpected case; King Alhomet, the son of Halys, he blooded excessively, it was autumn and he drank wine, and after sleep he drew three libra of blood. When I was called for him at night, I found him unconscious, his eyes staring upwards out of fear. I ordered five white dove chicks to be brought to me, and I ordered them to be properly prepared and caused the organs to separate themselves, I cooked them in four quarts of fragrant wine until the meat was separated from the bones. I added plenty of cloves and cinnamon to the decoction, then I filtered this decoction, I put it in a vessel with a pitcher spout, I served it to the king to drink, I started talking to [him] before sunrise, he drank this decoction for thirty days, he regained his former strength, his blood was completely back to normal.

6) Another unexpected case: The case, namely, the swelling near the brain, happened to King Errisideni, he was knowing and respecting me, I took three libra of blood from him until he lost consciousness with a frightening fainting, then I began to think, I anointed his body with galle, I put it on his nose, I tempered with a libra of fragrant wine, of a mixture of equal parts of chickens and pigeons, to which I had put musk, I shoved it into his mouth slowly. When he regained consciousness, his slaves had begun to weep. Some of them, looking sideways [side by side] made a plan for my death. Indeed, when the king came to life again, he told me that he did not feel much pain as long as he was unconscious from his own illness, but all his worries about me were carrying on for he feared that those standing next to him would bring me death. Also, unless he believes he's healthy, he was believing that I did not apply this treatment to him. That's why he ordered me never to take blood from him in front of anyone except the women around him. You should know that this king had survived a serious madness by this disease.

7) Another unexpected case about chronic discharge; a friend of mine, who is somewhat equipped in medicine, was disturbed by the discharge for a long time, and he frequently used many things for the discharge. He finally told me that they did not provide any benefit. So I stayed with him overnight to explain the cure for the disease and I understood, because he was more disturbed by the discharge after sleep, I realized that the cause of the disease was the hot humor that suddenly poured out of the brain and its flow intensified when it actually reached the stomach. He was really screaming in pain, there was no flow, he was constantly drooling, so I personally ordered him to shave his head with mustard and rub it vigorously with mugwort, and then he regained his health and never had a headache.

8) King Hamech, the son of Halys, had a stroke. In the beginning, there was no proper treatment, but they left him as he was, none of the physicians ordered anything else to be done to him except anointing and fumigating the body with fragrant things, I did not believe that it was enough for him, but I did get him to have to cup from his neck, he died quickly from that disease, in this case, self-confidence is a necessary state. If it happened to a person who is not weak-tempered and has a soft body, since this disease occurs in the neck, as we said before, it is necessary to

do cupping. I didn't want to do any of those things that some people recommended, but I put lotus oil on his nose.

9) I have helped many people suffering from heartburn and dryness get rid of many wounds with lotus oil and its syrup, I gave them to drink watery white wine moderated with snow water. I made them eat fatty chickens in which I put the moldy juices of quince seeds and lotus oil.

10) A well-intentioned friend of mine, who was studying the books of Galen with me, complained of pain in his stomach, and the pain increased as food passed through his stomach, I taught you to do these things, he told me he had made them before, I ordered him to take three ounces of rose sugar and the same amount of violet sugar, and I ordered these ingredients to be mixed well, in which I put half a muscal of amber and an ounce of lotus oil, and I mixed the oil in it, he used it, and he was cured of this disease by the permission of God.

11) Another unexpected case; I have cured many people of sun-induced fevers with lukewarm baths and cold water, and [the water] was so cold that the patient was afraid of it.

12) Another unexpected case: I have cured people with fatal latent fevers with the juice of laxative fruits and with sweet-smelling cold and temperate things, making them cold and moisturized, for if this cure had not been applied, the sick [person] would have succumbed to the disease.

13) Another unexpected case: Heatstroke happened to any person in summer, while he was out for a walk, a highly acute fever seized him, the temperature increased in him, he began to turn red in color, his very temperament changed, his illness became severe, his breath itself was very hot like fire, I personally examined him for signs of blood flow, he had heart palpitations. I looked carefully to see the blood flow, so I waited for an hour or two, believing that he would have some flow, nothing happened, I ordered him to rub his nose vigorously, no blood came out, the fever, impatience and pain began to increase in him. I therefore gave him ten libra of cold water, the fever subsided, he urinated a little, the fever began to subside, and yet the fever continued in him for forty days.

14) No one, out of concern for a slave, gave him water as he was given to his master, and he died before nightfall, the case happened in the morning. Although these cases have been mentioned before, still different accounts are recorded here and there, in some cases, this event is told more than it is, so we have taken care to include them here.

15) The great King Haamor, son of Halys, weakened spontaneously in the autumn, when in his drunkenness, the bandage on his forearm loosened, and much blood flowed out. I was taken to him at night, and found him himself unconscious, so strong that even though his eyes were open, not even his eyelids moved, then I ordered five young pigeons and five chickens to be slaughtered, cut into pieces, and boiled in three quarts of sweet wine until the bones were separated from the meat. I put musk, cloves and cinnamon, and drank the strained liquid from the oracle's bowl, and after a while his strength and memory returned to him, and he was told to take this medicine for thirty days until he could replace the blood he had lost.

16) The hot swelling near the ear again affects the great king, now I had become a very familiar and friendly person to him, and I ordered an intravenous blood draw in the amount of three libras from the king, who had fainted for a long time. I myself healed him without fear, anointed his body with gall, and sent much of it into his nose, and took a [libra] of sweet-smelling wine, and a [libra] of the broth of young pigeons and hens, and added fresh red musk, I personally sent it down his throat, he regained consciousness immediately, there is no doubt that he was saved from a strong madness/delirium thanks to this treatment, that is, by taking blood from the vein.

17) Haamel, the son of Halys, was paralyzed, and the physicians who were with him ordered to put scented things in his nose, but I did not find it appropriate. But I was happy to do cupping on the neck cavity, because it is useful for everyone who is not cold-tempered and has paralysis, and I did not need any other medicine other than putting lotus oil in the nose for acute migraine.

18) The person constantly complained of diarrhea, I ordered him to use the things he had used before. But they did not benefit, when I spent time with him, I saw that he did not sit in the chair all the time, except after a long sleep. Then his nature was constipating throughout the day, I asked him if he had diarrhea after night's sleep, he said it was, I realized that the humor went from his head to his stomach, moving the stomach to expel waste, he frequently spit saliva when he was awake, when I thought that the humor descended from there [the head] in sleep,

I ordered him to shave his head, rub it with mustard and spread the scent of mugwort, and the chronic diarrhea disappeared.

19) I have also saved many people from death who complained of dry stomach and fever by giving them lotus sugar and syrup and diluted white wine and the same amount of chilled water on the stomach. I was giving him cold, cooked chicken sprinkled with the sticky pulp of quinces and lotus oil.

20) I had a friend who complained of stomach ache, especially at the beginning of digestion. I took four ounces of violet and rose sugar, mixed it, added a ounce of aloe, and an ounce of lotus oil. I mixed it again and applied it to him personally until he completed the treatment and got better. I have always been satisfied with the earth bath with fresh hot water at Ephimera. Then I was always pleased with the cold water, the syrup of fruits with laxatives on a constant fire, always taking care not to expose it to pubescence, and using it in all kinds of fires, coldness and dampness. This is the treatment I applied to him when he was caught while walking in the summer, while returning, he caught an acute fever with very high temperature, but on the fourth day the fever increased, reddening of the bile, harmful symptoms appeared, the breath coming out of it was very hot, after an hour he had chest pain, when I saw all these symptoms occurring, I was expecting a runny nose or diarrhea, harmful things continued in the same situation, I ordered him to scratch his nose so that the delayed discharge could come, the temperature could increase, I gave him ten pounds of cold water, suddenly, hardness developed, the temperature decreased, he urinated, the fever continued like this for ten days, similarly his slave who was walking with him was also exposed to this same fever. But because he did not drink cold water, he died at the same time at noon of the same day. There is no doubt that the master was saved from death by drinking cold water.

21) Razi states: Because I am very enthusiastic about medicine, I had to stay sober, I did so until I was completely sleepless, I used different things that did not benefit me at all, I could not find anything better except putting lotus oil in the nose and eating the lettuce that I consumed throughout my youth. When I consumed it in my old age, I bought the slightly cooked ones. Then I developed poor eyesight and testicular weakness, I have found nothing better than to consume sparrows and pigeon chicks until sight is restored. I have found a perfect oil for this, the rest is nothing but trouble: pine oil, banyan oil, sweet apple oil must be taken from each of them, from the middle part of the sparrow's gall. All of them should be boiled over low heat until they boil over, then add half an ounce of red musk, lubricate the penis and testicles using after bathing, this oil stimulates and regulates strength. A young friend of mine, a Jerusalemite like myself, complained to me of heart trouble, sadness and fear for no known reason. I ordered him to ask for the meat of the falcon, sprinkled with rose water and roasted with basil and cloves. I ordered him to drink white wine instead of water and to smell fragrant things. I personally helped him gain courage and strength through this. Thus he was healed of the affliction. You should know that the old strength could not be obtained by regaining health and a little blood unless you consume pigeons, doves and sparrows along with fragrant wine.

DISCUSSION

First of all, it should be noted that cases one, two, six, seven, eight, 13, 18 and 21 were included in the discussion. In this chapter which Kuhne [25] states is the most praised section by western authors and whose two Latin editions confirm its popularity in Europe, Razi included the prescriptions he applied regarding his own complaints in cases one, two and 21. An autobiographical narrative appears in these cases. Temkin [19] emphasized that this autobiographical information is important if it is believed, as it provides information about Razi's blindness. In the fifth chapter of the second book of Galen' work *De Locis Affectis*, which consists of six books, between pages 69-135, it was seen that he described a severe pain that happened to him by saying "Ac memini mihi ipsi accidisse dolorem vehementissimum" (and I remembered an extremely severe pain that happened to me). Thinking that the cause of the pain was a stone in one of the ureters, he mentioned that he applied herbal treatment and the process of removing humour from the body. However, when he removed the humor from the body, he claimed that this pain was caused by the intestines, not the stone. It was also noticed that Galen used the first person singular of verbs such as 'excrevi' 'I emptied', 'putabam' 'I was thinking', 'conspexi' 'I observed'[38]. One of the points that parallels the case narratives of his predecessors is that in Razi's work, the patient groups include the king, his friend, slaves and citizens after him. Brain [39] reported in his study that Hippocrates treated poor people in different towns. Galen, on the other hand, in the fourth chapter of his ninth book, located between pages 599-660 of his work *Methodus Medendi* which consists of 14 books, describes the cases in which he dealt with two different young people, one free and the other a slave, with fever, showing his medical approaches and literary equipment: "Ac tibi exempli causa redigam in

memoriam adolescentes duos quos una mecum vidisti. Erat alter eorum liber et palaestrae peritus, alter servus haud inexercitatus ille quidem…"[40].

(However, I will remind you [Eugenianus] by way of example of the two young men you saw with me. One of them was free and experienced in wrestling, the other was a slave who was not really incapable...)

Galen gave priority to the free wrestler, and at the moment he encountered the patient, he described the patient's clinical condition and the pulse characteristics, which are considered among the vital indicators, "...Sed pulsus aequales et maximos et celeres et frequentes et vehementes..." "But the pulse is regular, loud, fast, frequent and violent…" and he described urine and its characteristics, which become physical indicators in the physician's evaluation of the patient, the foods he is accustomed to, fever, duration and type of fever, and the patient's follow-up at regular intervals [40]. Among the treatment options, it is among the findings that a treatment plan such as bloodletting and rest was made according to the needs of the patient [40].

In the context of the subject, Razi emphasizes that in his work titled *Aḥlāq al-Ṭabīb* being the physician of a statesman provides a high position for the physician increases his value, and that there will be no negative situations such as humiliation and playing with his honor [41].

It can be said that Razi continued to treat people from all classes of society, without deviating from social discrimination, by quoting Galen' approach, "What befits a physician is to treat the poor as well as the rich", in the chapter titled "The Necessity of Treating the Poor" in his work titled *Aḥlāq al-Ṭabīb* [41]. However, it is noteworthy that in the chapter titled "About the Cases That Happened to Razi's", he does not include women and children in the patient group. In this context, Razi emphasizes in the chapter titled "The Most Difficult Aspects of Medicine" of his work titled *Aḥlāq al-Ṭabīb* that one of the most difficult aspects of medical science is the treatment of women [41]. Meyerhof [21] refers to the impossibility of a comprehensive examination of Muslim female patients.

Another issue that needs to be addressed is that the psychological discomfort and the patient's careless lifestyle, drinking habits, fever, stomach pain, swelling in the ear, etc. identified in Razi's case narratives largely coincide with the information provided by his predecessors. In the chapter titled "About the Cases That Happened to Razi's" Razi, unlike his predecessors, did not include any narratives about pregnant women, childbirth, puerperium, and women's vaginal discharge. Another issue that does not overlap is that while Hippocrates almost never included treatment in his work titled *De Morbis Popularibus,* in Razi's work includes warm baths, cupping, rubbing, using laxatives, bloodletting and treatment with wine, in addition to the treatment prepared by him, especially with herbal and animal mixtures, in individualized cases.

On the other hand, in cases six, seven, 13 and 18, it was determined that the physician spent a certain period of time (until the morning or two hours) with the patient. As in the cases of Hippocrates in his work *De Morbis Popularibus*, the patient's clinic was not recorded day by day in Razi's work. It is among the information obtained that when the physician is called for the patient at night, the physician describes the patient's clinical condition at the scene, does not administer the medicine and leave the patient's side, on the contrary, he tries to understand the changes in the clinical condition by observing the patient and provides treatment based on the cause. In this respect, it can be said that Razi was selflessly towards his patients, showed care and spared time. In other words, it is possible to see traces of the physician's touch on human life in these cases. On the other hand, in the information given by Galen in his work *De Praecognitione*, it was found that both he and other physicians left the patient after administering the medicine to the patient [10].

In the sixth case, the presence of negative thoughts towards the physician as "Some of them planned my death with a side-eye" has been found. This case was found to be repeated in the chapter titled "The Humility of the Physician" in the book of *Aḥlāq al-Ṭabīb* of Razi [41]. It can be stated that this idea evokes the concept of violence against physicians, which is increasing today. In the continuation of this case, in the sentence "he (the king) commanded me never to take blood from him in front of anyone except the women around him", it has been determined that the king exhibited a protective attitude towards the physician, when considering the people working with the king as the relatives of the patient. Levey [42] in his study of Ruhavi's views, states that the statesmen valued physicians more than other people and based on this attitude on the grounds that the art of medicine was extremely useful for both the upper class and ordinary people.

Again, in the sixth case, the sentence "...unless he believed that he was healthy, [the king] was believing that I did not apply this treatment to him" indicates that the patient trusted the physician. Levey [42] under the title "On the Examination of Physicians" in chapter sixteen where he discusses Ruhavi's views, states that the examination of the physician is important and that medical mistakes are much more vital than mistakes made by people in other arts. For this reason, the harmony between the physician and the patient in the treatment of the disease is a situation that should be taken into account. In this regard, in the title "Humility of the Physician" of his work titled *Aḥlāq al-Ṭabīb*, Razi [41] states that the patient should obey the practices and directives of the physician when he needs the benefits of medicine.

Finally, in the eighth case, unlike the other physicians, Razi confidently applied a different treatment to the patient (cupping), and the chapter is enriched and shaped with findings such as instant clinical observations about the course of the diseases that are the subject of the cases throughout the chapter, the outcome of the disease with salah or death, the duration of treatment, and the use of ink medicines predominantly in the treatments.

CONCLUSION

To sum up, it has been noticed that in the case narratives presented by Razi, while the patient group consists of different people, cases based on complaints such as paralysis, swelling, heat stroke, discharge, stomach pain and burning are repeated. For example, swelling in cases six and 16, paralysis in cases eight and 17, stomach pain and burning in cases nine, 10 and 20, and sun-induced fever in cases 11 and 13 can be shown. In addition, it can be said that he structured the principles of medical ethics by being influenced by the approaches of Hippocrates and Galen, in terms of the physician examining the poor without discrimination and the feeling of trust between the physician and the patient. On the other hand, it would not be wrong to say that he was also influenced by his work titled *Aḥlāq al-Ṭabīb* which he wrote using the works of ancient physicians like Hippocrates and Galen. However, it does not go unnoticed that he sometimes acts boldly in the treatment of cases in which he describes the disease with his own clinical observation power and reduces it to individuality. Another point that should be underlined is that he tried to understand, diagnose and treat diseases through the symptoms of his predecessors, using the knowledge of his predecessors, and his contribution to the knowledge with the experiences he gained. When examined within the literary framework, it can be said that Razi's style is dominated by clarity, comprehensibility and simplicity, based on the way he narrates the case. Again, it can be said that the presence of short sentences in the narrative facilitates memorability.

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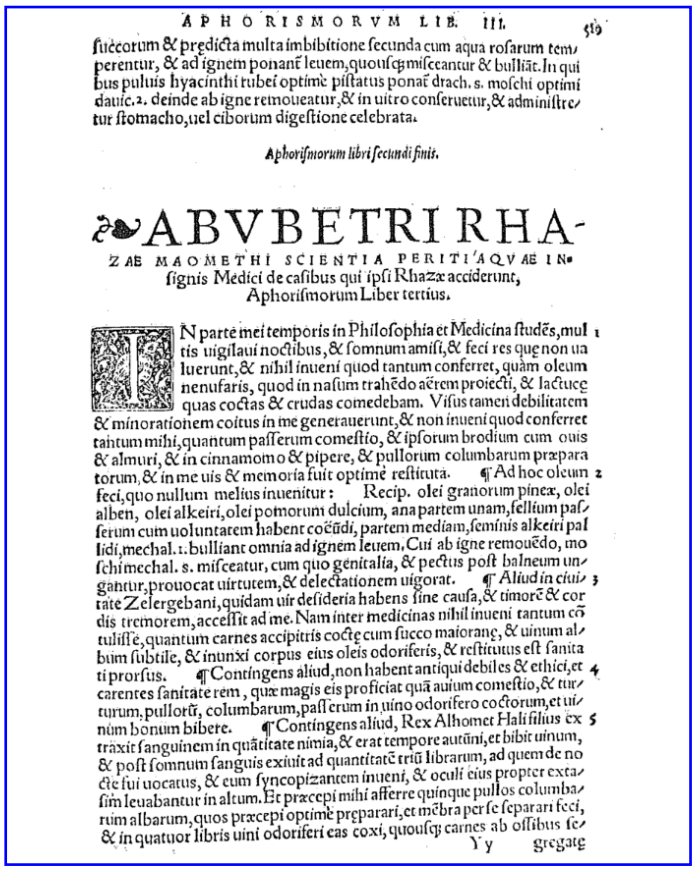
Yasar Soydan N, Aciduman A, Askit C, Arda B (2024) Abu Bakr Muhammad al-Razi's, a Distinguished Physician in Point of Knowledge and Experience, About the Cases. Eur J Ther. 30(6):910-922. https://doi.org/10.58600/eurjther2286

Annex-1. Original Latin Text



APHORISMORVM LIB. III. 519

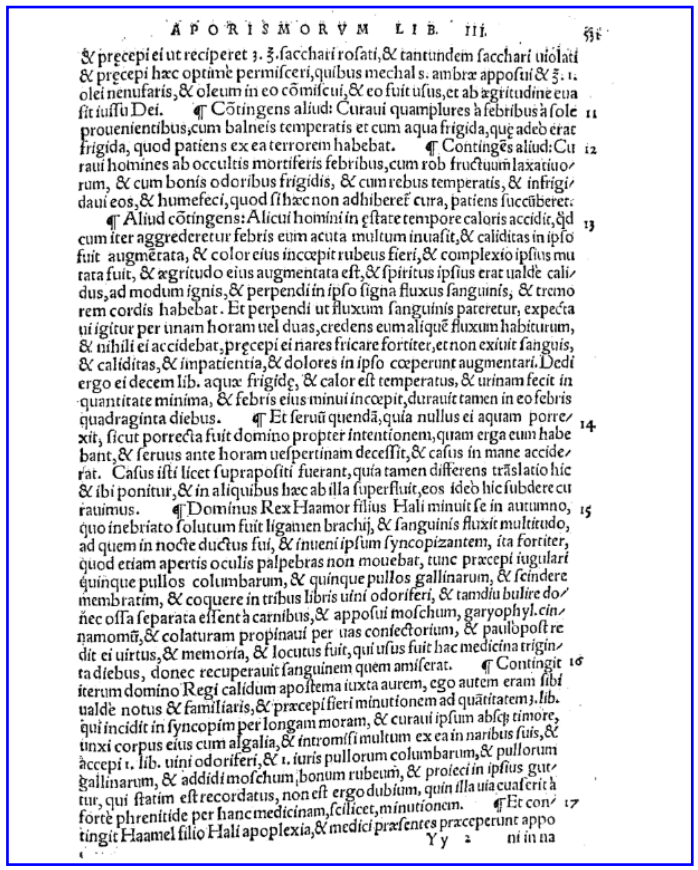
fuccorum & predicta multa imbibitione fecunda cum aqua rosarum temperentur, & ad ignem ponantē leuem, quousq; misceantur & bulliāt. In quibus puluis hyacinthi rubei optimè pistatus ponat drach. s. moschi optimi dauic. 2. deinde ab igne remoueatur, & in uitro conseruetur, & administretur stomacho, uel ciborum digestione celebrata.

Aphorismorum libri secundi finis.

ABVBETRI RHAZAE MAOMETHI SCIENTIA PERITI AQVAE IGnis Medici de casibus qui ipsi Rhazæ acciderunt, Aphorismorum Liber tertius.

IN parte mei temporis in Philosophia et Medicina studēs, multis uigilaui noctibus, & somnum amisi, & feci res quę non ualuerunt, & nihil inueni quod tantum conferret, quàm oleum nenufaris, quod in nasum trahēdo aērem proiecti, & lactucę quas coctas & crudas comedebam. Visus tamen debilitatem & minorationem coitus in me generauerunt, & non inueni quod conferret tantum mihi, quantum passerum comestio, & ipsorum brodium cum ouis & almuri, & in cinnamomo & pipere, & pullorum columbarum præparatorum, & in me uis & memoria fuit optimè restituta. ¶ Ad hoc oleum 2
feci, quo nullum melius inuenitur: Recip. olei granorum pinex, olei alben, olei alkeiri, olei pomorum dulcium, ana partem unam, sellium passerum cum uoluntatem habent coēūdi, partem mediam, seminis alkeiri pallidi, mechal. 1. bulliant omnia ad ignem leuem, Cui ab igne remouēdo, moschi mechal. s. misceatur, cum quo genitalia, & pectus post balneum ungantur, prouocat uirtutem, & delectationem uigorat. ¶ Aliud in ciui- 3
tate Zelergebani, quidam uir desideria habens sine causa, & timorē & cordis tremorem, accessit ad me. Nam inter medicinas nihil inueni tantum cō tulisse, quantum carnes accipitris coctę cum succo maiorane, & uinum album subtile, & inunxi corpus eius oleis odoriferis, & restitutus est sanitati prorsus. ¶ Contingens aliud, non habent antiqui debiles & ethici, et 4
carentes sanitate rem, quæ magis eis proficiat quā auium comestio, & turturum, pullorū, columbarum, passerum in uino odorifero coctorum, et uinum bonum bibere. ¶ Contingens aliud, Rex Alhomet Hali filius ex 5
traxit sanguinem in quātitate nimia, & erat tempore autūni, et bibit uinum, & post somnum sanguis exiuit ad quantitatē triū librarum, ad quem de nocte fui uocatus, & cum syncopizantem inueni, & oculi eius propter extasim leuabantur in altum. Et præcepi mihi afferre quinque pullos columbarum albarum, quos præcepi optimè preparari, et mēbra per se separari feci, & in quatuor libris uini odoriferi eas coxi, quousq; carnes ab ossibus se-

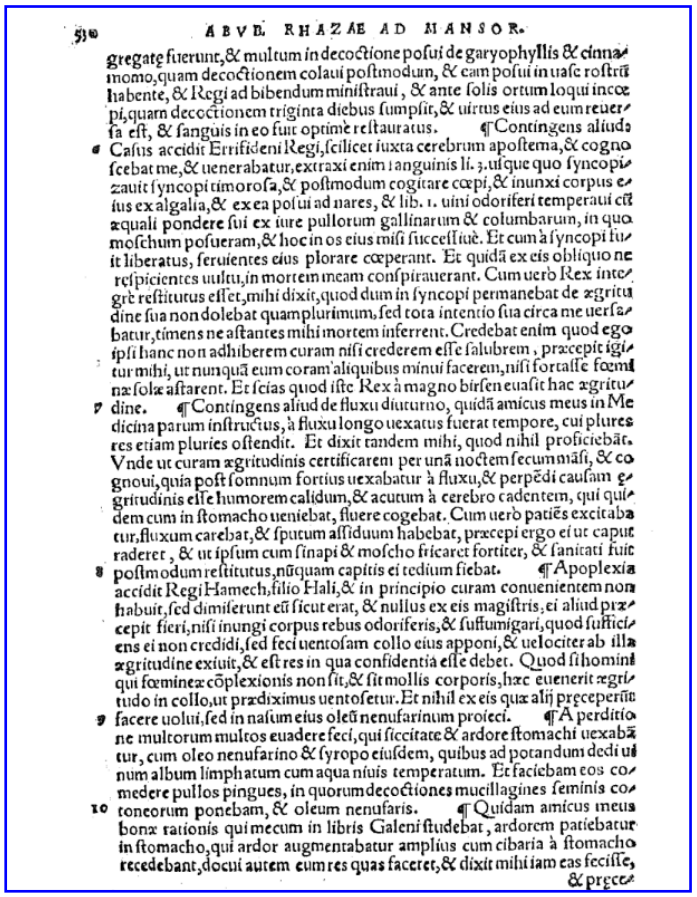
Yy gregate



APORISMORVM LIB. III. 521

& præcepi ei ut reciperet 3. 3. sacchari rosati, & tantundem sacchari uiolati & præcepi hæc optimè permisceri, quibus mechal s. ambræ appositi & 3. 1. olei nenufaris, & oleum in eo cōmisceri, & eo fuit usus, et ab ægritudine eua sit iussu Dei. ¶ Cōtingens aliud: Curaui quamplures à febribus à sole 11
prouenientibus, cum balneis temperatis et cum aqua frigida, quę adeò erat frigida, quod patiens ex ea terrorem habebat. ¶ Contingēs aliud: Cu- 12
raui homines ab occultis mortiferis febribus, cum rob fructuum laxatiuorum, & cum bonis odoribus frigidis, & cum rebus temperatis, & infrigidaui eos, & humefeci, quod sī hæc non adhiberē cura, patiens succūberet.
¶ Aliud cōtingens: Alicui homini in æstate tempore caloris accidit, & 13
cum iter aggrederetur febris eum acuta multum inuasit, & caliditas in ipso fuit augmētata, & color eius incœpit rubeus fieri, & complexio ipsius mutata fuit, & ægritudo eius augmentata est, & spiritus ipsius erat ualdè calidus, ad modum ignis, & perpendi in ipso signa fluxus sanguinis, & tremorem cordis habebat. Et perpendi ut fluxum sanguinis pateretur, expecta ui igitur per unam horam uel duas, credens eum aliquē fluxum habiturum, & nihil ei accidebat, præcepi ei nares fricare fortiter, et non exiuit sanguis, & caliditas, & impatientia, & dolores in ipso cœperunt augmentari. Dedi ergo ei decem lib. aquæ frigidę, & calor est temperatus, & urinam fecit in quantitate minima, & febris eius minui incœpit, duraut tamen in eo febris quadraginta diebus. ¶ Et seruū quendā, quia nullus ei aquam porre- 14
xit, sicut porrecta fuit domino propter intentionem, quam erga eum habebant, & seruus ante horam uespertinam decessit, & casus in mane accidérat. Casus isti licet suprapositi fuerant, quia tamen differens trāslatio hic & ibi ponitur, & in aliquibus hæc ab illa superfluit, eos ideò hic subdere curauimus. ¶ Dominus Rex Haamor filius Hali minuit se in autumno, 15
quo inebriato solutum fuit ligamen brachij, & sanguinis fluxit multitudo, ad quem in nocte ductus fui, & inueni ipsum syncopizantem, ita fortiter, quod etiam apertis oculis palpebras non mouebat, tunc præcepi iugulari quinque pullos columbarum, & quinque pullos gallinarum, & scindere membratim, & coquere in tribus libris uini odoriferi, & tamdiu bulire donec ossa separata essent à carnibus, & apposui moschum, garyophyl. cinamomū, & colaturam propinaui per uas confectorium, & paulò post redit ei uirtus, & memoria, & locutus fuit, qui usus fuit hac medicina triginta diebus, donec recuperauit sanguinem quem amiserat. ¶ Contingit 16
iterum domino Regi calidum apostema iuxta aurem, ego autem eram sibi ualdè notus & familiaris, & præcepi fieri minutionem ad quātitatem 3. lib. qui incidit in syncopim per longam moram, & curaui ipsum absq; timore, unxi corpus eius cum algalia, & intromisi multum ex ea in naribus suis, & accepi 1. lib. uini odoriferi, & 1. iuris pullorum columbarum, & pullorum gallinarum, & addidi moschum, bonum rubeum, & proieci in ipsius gutture, qui statim est recordatus, non est ergo dubium, quin illa uia euaserit à forte phrenitide per hanc medicinam, scilicet, minutionem. ¶ Et con- 17
tingit Haamel filio Hali apoplexia, & medici præsentes præceperunt appo-

Yy 2 ni in na



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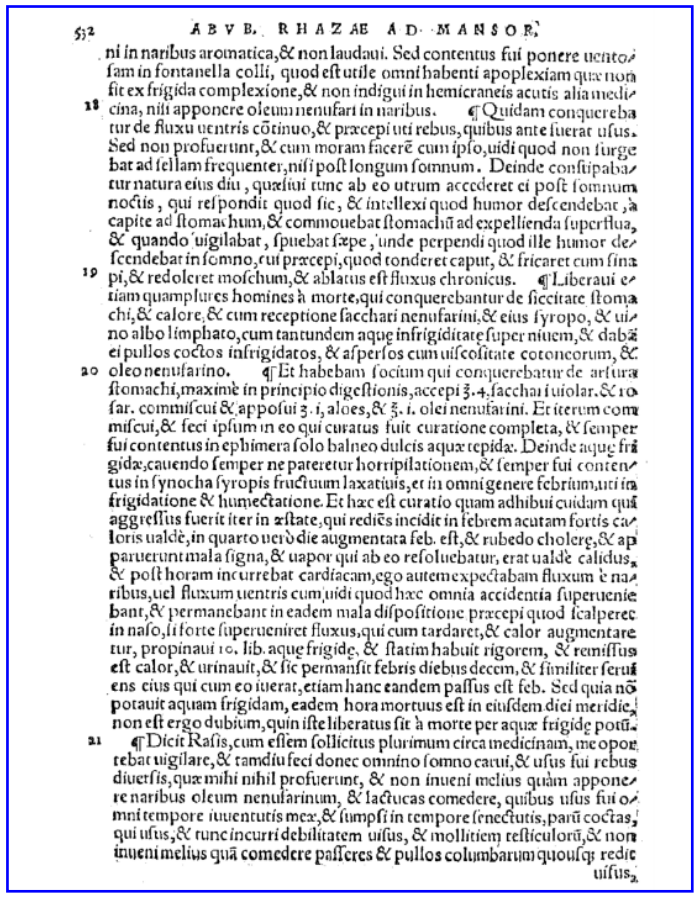
gregate fuerunt, & multum in decoctione posui de garyophyllis & cinnamomo, quam decoctionem colaui postmodum, & eam posui in uase rostrū habente, & Regi ad bibendum ministraui, & ante solis ortum loqui incœpi, quam decoctionem triginta diebus sumpsit, & uirtus eius ad eum reuersa est, & sanguis in eo fuit optimè restauratus. ¶ Contingens aliud: 6
Casus accidit Errifideni Regi, scilicet iuxta cerebrum apostema, & cognoscebat me, & uenerabatur, extraxi enim sanguinis li. 3. usque quo syncopizauit syncopi timorosa, & postmodum cogitare cœpi, & inunxi corpus eius ex algalia, & ex ea posui ad nares, & lib. 1. uini odoriferi temperati cū æquali pondere sui ex iure pullorum gallinarum & columbarum, in quo moschum posueram, & hoc in os eius misi successiuè. Et cum à syncopi fuit liberatus, seruientes eius plorare cœperant. Et quidā ex eis obliquo nec respicientes uultu, in mortem meam conspirauerant. Cum uerò Rex intergrè restitutus esset, mihi dixit, quod dum in syncopi permanebat de ægritudine sua non dolebat quamplurimum, sed tota intentio sua circa me uersabatur, timens ne astantes mihi mortem inferrent. Credebat enim quod ego ipsi hanc non adhiberem curam nisi crederem esse salubrem, præcepit igitur mihi, ut nunquā eum coram aliquibus minui facerem, nisi fortasse fœminæ solæ astarent. Et scias quod iste Rex à magno birsen euasit hac ægritu- 7
dine. ¶ Contingens aliud de fluxu diuturno, quidā amicus meus in Medicina parum instructus, à fluxu longo uexatus fuerat tempore, cui plures res etiam pluries ostendit. Et dixit tandem mihi, quod nihil proficiebat. Vnde ut curam ægritudinis certificarem per unā noctem secum māsi, & cognoui, quia post somnum fortius uexabatur à fluxu, & perpēdi causam ægritudinis esse humorem calidum, & acutum à cerebro cadentem, qui quidem cum in stomacho ueniebat, fluere cogebat. Cum uerò patiēs excitabatur, fluxum carebat, & sputum assiduum habebat, præcepi ergo ei ut caput raderet, & ut ipsum cum sinapi & moscho fricaret fortiter, & sanitati fuit 8
postmodum restitutus, nūquam capitis ei tedium fiebat. ¶ Apoplexia accidit Regi Hamech, filio Hali, & in principio curam conuenientem non habuit, sed dimiserunt eū sicut erat, & nullus ex eis magistris, ei aliud præcepit fieri, nisi inungi corpus rebus odoriferis, & suffumigari, quod sufficiens ei non credidi, sed feci uentosam collo eius apponi, & uelociter ab illa ægritudine exiuit, & est res in qua confidentia esse debet. Quod si homini qui fœmineæ cōplexionis non sit, & sit mollis corporis, hæc euenerit ægritudo in collo, ut prædiximus uentosetur. Et nihil ex eis quæ alij præceperūt 9
facere uolui, sed in nasum eius oleū nenufarinum proieci. ¶ A perditione multorum multos euadere feci, qui siccitate & ardore stomachi uexabātur, cum oleo nenufarino & syropo eiusdem, quibus ad potandum dedi unum album limpha tum cum aqua niuis temperatum. Et faciebam eos comedere pullos pingues, in quorum decoctiones mucillagines seminis co- 10
toneorum ponebam, & oleum nenufaris. ¶ Quidam amicus meus bonæ rationis qui mecum in libris Galeni studebat, ardorem patiebatur in stomacho, qui ardor augmentabatur amplius cum cibaria à stomacho recedebant, docui autem eum res quas faceret, & dixit mihi iam eas feciſſe,

& præce-



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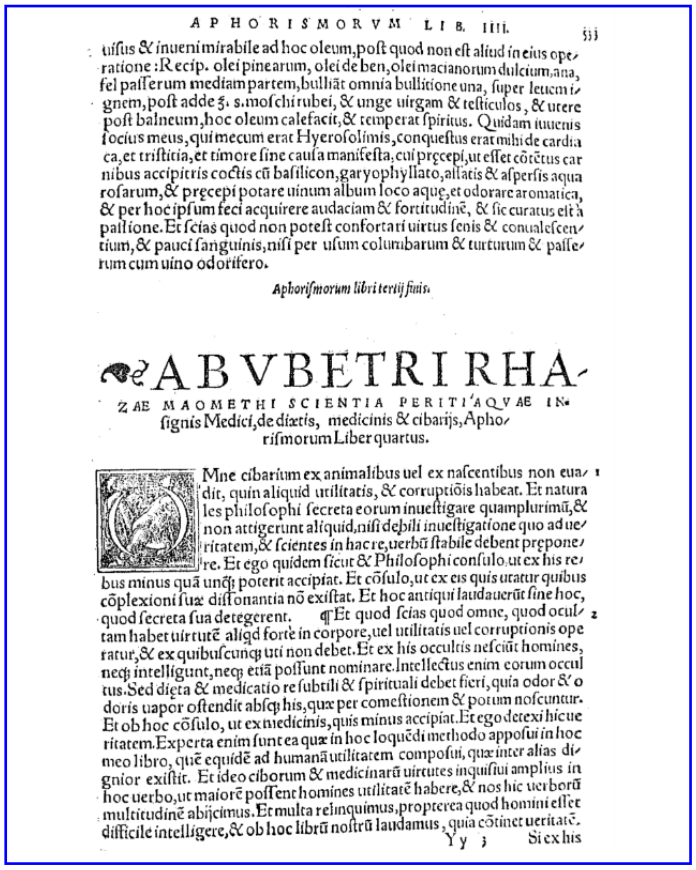
ni in naribus aromatica, & non laudaui. Sed contentus fui ponere uentosam in fontanella colli, quod est utile omni habenti apoplexiam quæ non fit ex frigida complexione, & non indigui in hemicraneis acutis alia medi- 18
cina, nisi apponere oleum nenufari in naribus. ¶ Quidam conquerebatur de fluxu uentris cōtinuo, & præcepi uti rebus, quibus ante fuerat usus. Sed non profuerunt, & cum moram facerē cum ipso, uidi quod non surgebat ad sellam frequenter, nisi post longum somnum. Deinde constipabatur natura eius diu, quæsiui tunc ab eo utrum accederet ei post somnum noctis, qui respondit quod sic, & intellexi quod humor descendebat à capite ad stomachum, & commouebat stomachū ad expellienda superflua, & quando uigilabat, spuebat sæpe, unde perpendi quod ille humor descendebat in somno, cui præcepi, quod tonderet caput, & fricaret cum sina- 19
pi, & redoleret moschum, & ablatus est fluxus chronicus. ¶ Liberaui etiam quamplures homines à morte, qui conquerebantur de siccitate stomachi, & calore, & cum receptione sacchari nenufarini, & eius syropo, & uino albo limphato, cum tantundem aquę infrigiditate super niuem, & dabā ei pullos coctos infrigidatos, & aspersos cum uisco situate cotoneorum, & 20
oleo nenufarino. ¶ Et habebam socium qui conquerebatur de arsura stomachi, maximè in principio digestionis, accepi 3. 4. sacchari uiolar. & rosar. commisci & apposui 3. i, aloes, & 3. i. olei nenufarini. Et iterum commisci, & feci ipsum in eo qui curatus fuit curatione completa, & semper fui contentus in ephimera solo balneo dulcis aquæ tepidæ. Deinde aquę frigidæ, cauendo semper ne pateretur horripilationem, & semper fui contentus in syncha syropis fructuum laxatiuis, et in omni genere febrium, uti infrigidatione & humectatione. Et hæc est curatio quam adhibui cuidam qui aggressus fuerit iter in æstate, qui rediēs incidit in febrem acutam fortis caloris ualdè, in quarto uerò die augmentata feb. est, & rubedo cholerę, & apparuerunt mala signa, & uapor qui ab eo resoluebatur, erat ualdè calidus, & post horam incurrebat cardiacam, ego autem expectabam fluxum è naribus, uel fluxum uentris cum uidi quod hæc omnia accidentia superueniebant, & permanebant in eadem mala dispositione præcepi quod scalperet in naso, si forte superueniret fluxus, qui cum tardaret, & calor augmentaretur, propinaui 10. lib. aquę frigidę, & statim habuit rigorem, & remissus est calor, & urinauit, & sic permansit febris diebus decem, & similiter seruiens eius qui cum eo iuerat, etiam hanc eandem passus est feb. Sed quia nō potauit aquam frigidam, eadem hora mortuus est in eiusdem diei meridie, non est ergo dubium, quin iste liberatus sit à morte per aquæ frigidę potū.
¶ Dicit Rasis, cum essem sollicitus plurimum circa medicinam, me opor- 21
rebat uigilare, & tamdiu feci donec omnino somno carui, & usus fui rebus diuersis, quæ mihi nihil profuerunt, & non inueni melius quàm apponere naribus oleum nenufarinum, & lactucas comedere, quibus usus fui omni tempore iuuentutis meæ, & sumpsi in tempore senectutis, parū coctas, qui usus, & nunc incurri debilitatem usus, & mollitiem testiculorū, & non inueni melius quā comedere passeres & pullos columbarum quousq; redit

usus,

Annex-1. Original Latin Text



APHORISMORVM LIB. IIII. 533

uissus & inuenimirabile ad hoc oleum,post quod non est alitud in eius ope-
ratione :Recip. olei pinearum, olei de ben, olei macianorum dulcium,ana,
fel passerum mediam partem,bullīāt omnia bullitione una, super leucim i-
gnem,post adde ʒ. s.moschi rubei, & unge uirgam & testiculos, & utere
post balneum,hoc oleum calefacit,& temperat spiritus. Quidam iuuenis
socius meus,qui mecum erat Hyerosolimis,conquestus erat mihi de cardia
ca,et tristitia,et timore sine causa manifesta,cui precepi,ut esset cōtectus car
nibus accipitris coctis cū basilicon,garyophyllato,allatis & aspersis aqua
rosarum,& precepi potare uinum album loco aquę,et odorare aromatica,
& per hoc ipsum feci acquirere audaciam & fortitudinē, & sic curatus est a
passione. Et scias quod non potest confortari uirtus senis & conualescen-
tium,& pauci sanguinis,nisi per usum columbarum & turturum & passe-
rum cum uino odorifero.

Aphorismorum libri tertij finis.

ABVBETRI RHA-

ZAE MAOMETHI SCIENTIA PERITI AQVAE IN-
signis Medici,de diætis, medicinis & cibarijs,Apho-
rismorum Liber quartus.

Mne cibarium ex animalibus uel ex nascentibus non euā- 1
dit, quin aliquid utilitatis, & corruptiōis habeat. Et natura
les philosophi secreta eorum inuestigare quamplurimū,&
non attigerunt aliquid,nisi debili inuestigatione quo ad ue-
ritatem,& scientes in hac re,uerbū stabile debent prepone-
re. Et ego quidem sicut & Philosophi consulo,ut ex his re-
bus minus quā unctę poterit accipiat. Et cōsulo,ut ex eis quis utatur quibus
cōplexioni suæ dissonantia nō existat. Et hoc antiqui laudauerūt sine hoc,
quod secreta sua detegerent. ¶Et quod scias quod omne, quod oculā- 2
tam habet uirtutē aliqd forte in corpore,uel utilitatis uel corruptionis ope
ratur,& ex quibuscunq uti non debet. Et ex his occultis nescīūt homines,
neq; intelligunt,neq; etiā possunt nominare. Intellectus enim eorum occul
tus. Sed dieta & medicatio re subtili & spirituali debet fieri, quia odor & o
doris uapor ostendit absq; his,quæ per comestionem & potum noscuntur.
Et ob hoc cōsulo, ut ex medicinis, quis minus accipiat. Et ego detexi hic ue
ritatem. Experta enim sunt ea quæ in hoc loquēdi methodo apposui in hoc
meo libro, quē equidē ad humanā utilitatem composui, quæ inter alias di-
gnior existit. Et ideo ciborum & medicinarū uirtutes inquisiui amplius in
hoc uerbo,ut maiorē possent homines utilitatē habere,& nos hic uerborū
multitudinē abijcimus. Et multa relinquimus,propterea quod homini esset
difficile intelligere,& ob hoc librū nostrū laudamus, quia cōtinet ueritatē.

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Letter to Editor

Unexpected Falls in Schizophrenia: Clozapine-Induced Negative Myoclonus

Mustafa Karaağaç[1]

[1] Department of Psychiatry, Faculty of Medicine, Karamanoglu Mehmetbey University, Karaman, Turkiye

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Corresponding Author
Mustafa Karaağaç, MD
Address: Department of Psychiatry, Faculty of Medicine, Karamanoglu Mehmetbey University, Karaman, Turkiye
E-mail: mustafakaraagac@kmu.edu.tr

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ABSTRACT

Myoclonus, characterized by sudden involuntary muscle contractions, can occur in a variety of conditions, including as a side effect of clozapine, which is used in the treatment-resistant schizophrenia. This case study describes a 48-year-old female patient who developed negative myoclonus, manifested by knee flexion and falls, after starting clozapine. Despite dose reduction and the addition of valproic acid, symptoms persisted, highlighting the dose-dependent nature of clozapine-induced myoclonus and the need for clinicians to recognise this risk.

Dear Editor,

Myoclonus is defined as a sudden, involuntary contraction of a muscle or muscle group. It can be observed in a number of different pathological conditions, including neurodegenerative, systemic metabolic and central nervous system diseases [1]. Negative myoclonus is a motor phenomenon characterized by involuntary contraction due to short, sudden inhibition of muscle activity.

Since there is insufficient evidence supporting antipsychotic polypharmacy in patients with schizophrenia who have not responded to other antipsychotic monotherapy treatments, clozapine monotherapy is recommended for treatment-resistant patients [2]. The presence of serious side effects, including agranulocytosis, myocarditis and seizures, represents a significant limit to its use. Clozapine-induced seizures manifest as either generalized tonic-clonic or myoclonic seizures, which may in turn precipitate the onset of generalized seizures [3].

Clozapine-induced myoclonus may manifest as either spasmodic muscle contractions (positive myoclonus) or a brief delay in muscle activity (negative myoclonus) [4]. Negative myoclonus presents as bending of the knees or folding of the legs. This article presents the case of a 48-year-old female patient with treatment-resistant schizophrenia who developed negative myoclonus with knee-folding attacks following clozapine treatment.

About Patient

A 48-year-old patient with a four-year history of schizophrenia and a history of significant extrapyramidal system adverse effects associated with low-dose aripiprazole and risperidone treatments was admitted to the psychiatry clinic for the initiation of clozapine treatment. The patient was commenced on a treatment regimen comprising 25 mg of clozapine per day. The dose was titrated with weekly hematological monitoring. Upon increasing the dosage of clozapine to 75 mg/day, pronounced rigidity was observed in both upper extremities. Consequently, the clozapine treatment was terminated. Following the cessation of clozapine therapy, psychotic symptoms manifested an exacerbation, prompting the reinitiation of clozapine treatment at a dosage of 150 mg/day. At a dosage of 150 mg/day, remission of psychotic symptoms was achieved; however, the patient began to experience involuntary and sudden folding of the knees, falling attacks, and difficulty in climbing stairs. A consultation was held with a neurologist, who considered the possibility of clozapine-induced negative myoclonus. No significant pathological findings were identified in the routine whole blood examination, extensive biochemistry analysis or brain MRI. Valproic acid 1000 mg/day was introduced due to the presence of diffuse spike-wave patterns on the electroencephalogram (EEG). Serum valproic acid levels were measured at 95 µg/mL, which is within the therapeutic range (50-100 µg/mL) commonly associated with effective seizure control and the management of myoclonus. At 150 mg/day of clozapine, the patient experienced persistent and pronounced myoclonic symptoms, which diminished upon dose reduction to 100 mg/day. The patient was discharged with the current treatment plan and referred to an outpatient clinic for follow-up.

DISCUSSION

The aetiology of clozapine-induced myoclonus remains uncertain. Desarkar et al. [5] have proposed that abnormalities in neurotransmitter systems, including the orexin system, may play a role in clozapine-induced negative myoclonus. Other potential mechanisms include the anticholinergic activity of clozapine, as observed in the context of epileptic seizures. Despite the dearth of sufficient studies of sufficient quality, it has been reported that clozapine-induced myoclonus may be dose-dependent [1] or, more likely, serum concentration-dependent [6]. In our patient, a decrease in knee folding was observed after the clozapine dose was reduced, supporting this finding. Although antiepileptic treatment is also recommended for the management of clozapine-induced myoclonus, it is noteworthy that no improvement was observed with valproic acid treatment in this case [2]. This finding suggests that valproate treatment may not prevent clozapine-induced myoclonus, as previously reported in two cases [7, 8]. Although clozapine-induced hypotension is readily identifiable by clinicians, it is also important to consider the potential for falls resulting from clozapine-induced negative myoclonus.

CONCLUSION

This case study highlights the necessity for the recognition of clozapine-induced myoclonus as a potential cause of falls in patients. Further research is required to investigate effective management strategies, as current standard treatments, such as valproic acid, may not be consistently effective in preventing these symptoms.

Yours sincerely,

Author Contributions: Conception: M.K. - Design: M.K. - Supervision: M.K. - -Materials: M.K. - Data Collection and/or Processing: M.K. - Analysis and/or Interpretation: M.K. - Literature: M.K. - Review: M.K. - Writing: M.K. - Critical Review: M.K.

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Letter to Editor

Cough Induced Rib Fracture in Pregnant Patient: Role of Ultrasound

Cemre Özenbaş[1,*], Hakan Koca[2]

[1] Department of Radiology, Private Buca Hospital, Tınaztepe University, İzmir, Turkiye
[2] Department of Pulmonology, Private Buca Hospital, Tınaztepe University, İzmir, Turkiye

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Corresponding Author
Cemre Özenbaş, MD, PhD
Address: Department of Radiology, Private Buca Hospital, Tınaztepe University, İzmir, Turkiye
E-mail: cozenbas@hotmail.com

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Dear Editor,

Cough induced rib fractures during pregnancy are rare and pose unique diagnostic challenges due to the need for minimizing fetal radiation exposure. We present a case of 30 years old pregnant woman in her third trimester who experienced acute chest pain following a severe cough episode. Due to potential risks associated with radiographic imaging, a chest ultrasound was utilized, effectively identifying a fracture in the right 10th rib. This case underscores the critical role of ultrasound in safely and accurately diagnosing rib fractures in pregnant patients, offering a reliable and radiation-free alternative to traditional imaging methods.

A 30-year-old female patient who was 27 weeks pregnant presented with acute chest pain following a severe cough episode. She has no known disease and no abnormal findings were found during routine checks during her pregnancy. The examination revealed no findings other than tenderness in the right upper quadrant. An increase in WBC (11.83 10^3/uL) and CRP (22 mg/L) values was detected in laboratory tests. Laboratory values were thought to be due to upper respiratory tract infection and ultrasonography was performed for right upper quadrant pain. Liver echogenicity and size, gallbladder and right kidney were evaluated as normal in abdominal ultrasonography. In the examination performed with superficial probe on the local area where pain was described, discontinuity and stepping signs were observed in the outer contour of the right 10th rib (Figure 1). It was determined that the patient's pain increased when light pressure was applied with the probe to the location where these findings were found. As a result of the examination and ultrasonography findings, a diagnosis of rib fracture was made. No hematoma or space-occupying lesion was detected in the surrounding tissues. No signs of fracture were detected by ultrasonography in the 9th and 11th ribs or the other ribs. Medical treatment was given to the patient who had a single rib fracture and no examination or ultrasonography findings suggestive of pneumothorax.

Rib fractures are the most common type of injury in chest wall blunt trauma [1]. Even lower energy traumas can cause fractures, especially in older individuals [2]. Patients with rib fractures often feel pain, dyspnea, and in more extreme cases, consequences including

hemothorax, pneumothorax, or lung contusions. As the number of broken ribs increases, the risk of mortality also increases [3]. Compared to rib fractures caused by trauma, cough-related fractures are a rare but significant condition in the literature. Severe and recurring coughs can cause fractures under mechanical stress, especially in individuals with lung diseases such as chronic obstructive pulmonary disease or asthma [4]. Increased intra-abdominal pressure and osteogenic state have been suggested as the etiology of cough-related fractures in pregnant women [5]. Since rib fractures in pregnant women carry potential risks for the mother and the fetus, it's critical to diagnose them promptly and precisely.

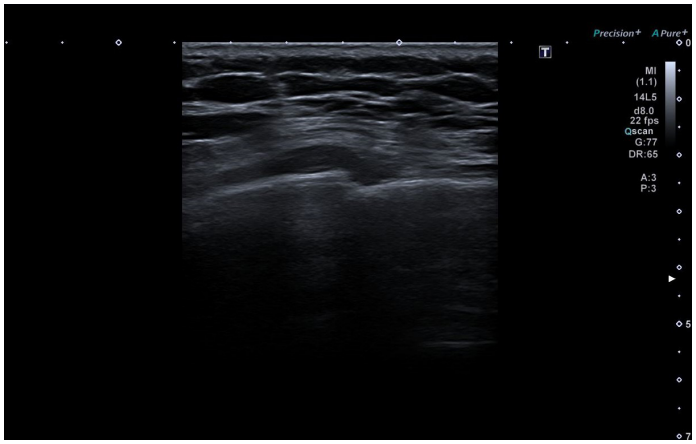

Figure 1. Cortical discontinuity and stepping sign in the ultrasonographic examination of right 10th rib with linear probe

Chest radiography is the first step in imaging, but trauma-related pathologies were detected in approximately half of the normal radiographs in Computed Tomography (CT) scan [6]. For this reason, CT is considered the gold standard in the diagnosis of rib fractures. However, its use is limited in sensitive populations such as pregnant women due to radiation exposure. In this context, ultrasonography can play an important role in diagnosis because it does not contain radiation and is easily applicable. In their systemic review, Yousefifard et al. [7] found the sensitivity of ultrasonography in the diagnosis of rib fracture to be 94% and the specificity to be 97%. This case report highlights the critical role of ultrasonography in the diagnosis of rib fractures in pregnant patients. Given its radiation-free nature, rapid and reliable results, ultrasonography should be the first-line imaging choice in the suspicion of rib fracture during pregnancy. The ease of use and high accuracy of ultrasonography provide significant advantages, especially when the use of radiographic and tomographic methods is limited. Wider adoption of ultrasonography for evaluating rib fractures in pregnant patients will enhance patient safety and prevent unnecessary radiation exposure.

Your sincerely.

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CORRECTION

Correction to: Biostatistics Leader in Türkiye from the Eyes of His Students: Prof. Kadir Sümbüloğlu

Seval Kul[1], İlkay Doğan[1,*], Ayşe Balat[2], Bektaş Açıkgöz[3], Zeliha Nazan Alparslan[4], Alper Serçelik[5], Mustafa Berhuni[6]

[1] Department of Biostatistics, Gaziantep University School of Medicine, Gaziantep, Türkiye
[2] Department of Pediatric Nephrology and Rheumatology, Gaziantep University School of Medicine, Gaziantep, Türkiye
[3] Retired Professor, Department of Neurosurgery, Zonguldak Bülent Ecevit University, Medical Faculty, Zonguldak, Türkiye
[4] Retired Professor, Department of Biostatistics, Çukurova University School of Medicine, Adana, Türkiye
[5] Department of Cardiology, SANKO University School of Medicine, Gaziantep, Türkiye
[6] Department of Ophthalmology, Gaziantep Provincial Health Directorate Dr. Ersin Arslan Education Research Hospital, Gaziantep, Türkiye

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Corresponding Author
İlkay Doğan, PhD
Address: Department of Biostatistics, Gaziantep University School of Medicine, 27310, Gaziantep, Türkiye
E-mail: ilkay_dgn58@hotmail.com

The sixth and seventh author's affiliation was published incorrectly in the original version of this article [1]. The authors' affiliations are as follows:

Alper Serçelik
Department of Cardiology, SANKO University School of Medicine, Gaziantep, Türkiye

Mustafa Berhuni
Department of Ophthalmology, Gaziantep Provincial Health Directorate Dr. Ersin Arslan Education Research Hospital, Gaziantep, Türkiye

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