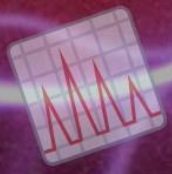
ISSN 2757-847X | e-ISSN 2718-0964

EAMS

Experimental and Applied Medical Science



Official Journal of Gaziantep Islam Science and Technology University, Faculty of Medicine

December 2022 , Volume 3, Issue 3

GAZİANTEP İSLAM BİLİM VE TEKNOLOJİ ÜNİVERSİTESİ TIP FAKÜLTESİ

GAZİANTEP ISLAM SCIENCE AND TECHNOLOGY UNIVERSITY FACULTY OF MEDICINE

Experimental and Applied Medical Science

Volume 3, Issue 3

Official Journal of Gaziantep Islam Science and Technology University, Faculty of Medicine

ISSN: 2757-847X e-

ISSN: 2718-0964

Contact information:

Gaziantep Islam Science and Technology University, Faculty of Medicine
Beştepe neighbouhood, Street number 192090 6/1 27010 Şahinbey/Gaziantep
Tel: +90 342 909 7500
E-mail: eams@gibtu.edu.tr

Dizinler/Indexing

Türkiye Atıf Dizini, Türk Medline, Google Scholar, Europub, Scilit, ASOS indeks, Advanced Science Index, Academic Resource Index, Eurasian Scientific Journal Index, Crossref, General Impact Factor

Published quarterly.

3 (üç) ayda bir yayınlanır.

Publishing date: 31.12.2022
Yayın tarihi: 31.12.2022

Owner/İmtiyaz Sahibi

On behalf of the Medical Faculty of Gaziantep Islam Science and Technology University
Gaziantep İslam Bilim ve Teknoloji Üniversitesi Tıp Fakültesi adına

Mediha Begüm KAYAR, Asst. Prof.

Chief Editor/Baş Editör

Hamit YILDIZ, Assoc. Prof.

Clerk of Editorial Office/Sorumlu Yazı İşleri Müdürü

Mehmet Göl, Asst. Prof.

Aim

Experimental and Applied MedicalScience aims at being a current and easily accessible academic publication in which striking research results that will improve the quality of life and are unique from every field of medical sciences are presented.

Scope

Experimental and Applied MedicalScience is an open-access, internationally double-blind peer reviewed academic medical journal and published in English four times a year, under the auspices of Medical Faculty of Gaziantep Islam Science and Technology University. The journalreceives manuscripts for consideration to be publishing in the form of research articles, reviews, letter to editor, briefnotification, summary notification etc.which could have been presented from within the country or abroad and including experimental animal studies related to the pathogenesis of diseases, pharmacological, clinical, epidemiological and deontological studies, also studies in the fields of improving public health, health services or health insurance. During evaluation or publication no charge is demanded from authors.

The journal is published every 3 months (March, July, September and December) with 4 issues per year. The literary language of the journal is English. Abstract part of the manuscript only should also be submitted in Turkish.

Amaç

Experimental and Applied Medical Science, yaşam kalitesini arttıracak çarpıcı araştırma sonuçlarının sunulduğu, tıp bilimlerinin her alanında benzersiz, güncel ve kolay erişilebilir bir akademik yayın olmayı hedeflemektedir.

Kapsam

Experimental and Applied Medical Science, Gaziantep İslam Bilim ve Teknoloji Üniversitesi Tıp Fakültesi himayesinde yılda dört kez İngilizce olarak yayınlanan açık erişimli, uluslararası çift kör hakemli bir akademik tıp dergisidir. Dergi, yurt içinden veya yurt dışından, hastalık patogenezleri ile ilişkili deneysel hayvan çalışmalarını, klinik, farmakolojik, epidemiyolojik, deontolojik çalışmalar ile beraber halk sağlığının geliştirilmesi amacı taşıyan ve sağlık hizmetleri veya sağlık sigortaları konularında araştırma makalelerini, derlemeleri, vaka sunumlarını, kısa bildirimleri, özet bildirimleri vs. yayınlamak için değerlendirmeye kabul etmektedir.

Değerlendirme veya yayın sırasında yazarlardan herhangi bir ücret talep edilmez.

Dergi 3 ayda bir (Mart, Temmuz, Eylül ve Aralık) yılda 4 sayı olarak yayımlanır. Derginin yazı dili İngilizcedir. Makalenin sadece özet kısmı Türkçe olarak da gönderilmelidir.

Ethical Principles and Publication Policy

Manuscripts are only considered for publication provided that they are original, not under consideration simultaneously by another journal, and have not been previously published. Direct quotations, tables, or illustrations that have extracted from any copyrighted material must be accompanied by written authority for their use from the copyright owners. All manuscripts are subject to review by the editors and referees. Deserving to be publishing is based on significance, and originality of the material. If anymanuscript is considered to deserve publishing, it may be subject to editorialrevisions to aid clarity and understanding without changing the data presented.

Experimental and Applied Medical Science strictly adheres to the principles set forth by "Helsinki Declaration" whose web address is indicated below. https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210525133548_b192cec0.pdf

Editorial Board declares that all reported or submitted studies conducted with "human beings" should be in accordance with those principles.

Manuscripts presenting data obtainedfrom a study design conducted with human participants must contain affirmation statements in the *Material and Methods* section indicating approval of the study by the institutional ethical review committee and "informed consent" was obtained from each participant. Also all manuscripts reporting experiments in which laboratory animals have been used should include an affirmation statement in the *Material and*

Etik İlkeler ve Yayın Politikası

Makaleler, orijinal/özgün olmaları, eş zamanlı olarak başka bir dergi tarafından incelenmemeleri ve daha önce yayınlanmamış olmaları koşuluyla yayına kabul edilebilmesi için değerlendirmeye alınır. Telif hakkıyla korunan herhangi bir materyalden alınan doğrudan alıntılar, tablolar veya resimler, kullanımları için telif hakkı sahiplerinden alınan yazılı izinle birlikte sunulmalıdır. Tüm yazılar editörler ve hakemler tarafından incelemeye tabidir. Yayınlanmaya hak kazanılması, materyalin önemine ve özgünlüğüne bağlıdır. Herhangi bir makalenin yayınlanmayı hak ettiği düşünülürse, sunulan veriler değiştirilmeden netlik ve anlayışa yardımcı olmak için editör revizyonlarına tabi tutulabilir.

Experimental and Applied Medical Science internet adresi aşağıda yer alan "Helsinki Deklarasyonu" ile belirlenen ilkelere sıkı sıkıya bağlıdır. https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210525133548_b192cec0.pdf

Editör Kurulu, "insan" ile yapılan tüm raporlanan veya sunulan çalışmaların bu ilkelere uygun olması gerektiğini beyaneder. İnsan katılımcılarla yürütülen bir çalışma tasarımından elde edilen verileri sunan makaleler, *Gereç ve Yöntemler* bölümünde çalışmanın kurumsal etik inceleme komitesi tarafından onaylandığını ve her katılımcıdan "bilgilendirilmiş onam" alındığını belirten onay ifadeleri kullanmalıdır. Ayrıca laboratuvar hayvanlarının kullanıldığı deneyleri bildiren tüm yazılar, *Gereç ve Yöntemler*

Methods section validating that all animals have received human care in compliance with the "Guide for the Care and Use of Laboratory Animals" whose web address is below and reveal approval by the institutional ethical review board. https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210818130308_dca61056.pdf

If there is a commercial relation that contributes to the study process or an institution that provides financial support; the authors must declare that either they have no commercial relationship with the commercial product, drug, company used, or what kind of relationship (consultant or any other agreement) they have, if any.

Processing and publication processes are free of charge. Any fee can not be requested from the authors during the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at https://dergipark.org.tr/tr/pub/eams. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Medical Faculty of Gaziantep Islam Science and Technology University. Potential advertisers should contact with the publishing office. Advertisement images are published only upon the Chief Editor's approval.

All researchers should have contributed to the article directly either academically or scientifically. Authors should have contributed either one or a few of planning, performing, writing or reviewing of manuscript. All authors should approve the final version. It is the authors'

bölümünde, internet adresi aşağıda belirtilmiş olan "Laboratuvar Hayvanlarının Bakımı ve Kullanımı Kılavuzu"na uygun olarak tüm hayvanların insanî bir bakım aldığını doğrulayan bir beyan ile kurumsal etik inceleme kurulunun onayını içermelidir.

https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210818130308_dca61056.pdf

Çalışma sürecine katkı sağlayan ticari bir ilişki veya çalışmaya maddi destek sağlayan bir kurum varsa; yazarlar ticari ürün, ilaç, aracılık eden şirket ile ticari bir ilişkilerinin olmadığını veya varsa ne tür bir ilişkisi (danışmanlık veya başka bir anlaşma) olduğunu beyan etmelidir.

Değerlendirme ve yayınlama süreçleri ücretsizdir. Değerlendirme ve yayın sürecinin hiçbir aşamasında yazarlardan ücret talep edilmez. Tüm yazılar https://dergipark.org.tr/tr/pub/eams adresinde bulunan çevrimiçi başvurusistemi üzerinden gönderilmelidir. Dergi ile ilgili kullanım kılavuzları, teknik bilgiler ve gerekli formlar derginin internet sayfasında yer almaktadır.

Derginin tüm masrafları Gaziantep İslam Bilim ve Teknoloji Üniversitesi Tıp Fakültesi tarafından karşılanmaktadır. Reklam vermeyi düşünen kişi veya kurumlar yayın ofisi ile iletişime geçmelidir. Reklam görselleri sadece Baş Editör'ün onayı ile yayınlanabilir.

Tüm araştırmacılar, makaleye doğrudan akademik veya bilimsel olarak katkıda bulunmuş olmalıdır. Yazarlar, makalenin planlanması, uygulanması, yazılması veya gözden geçirilmesi aşamalarından birine veya birkaçına katkıda bulunmuş olmalıdır. Tüm yazarlar nihai versiyonu onaylamalıdır. Bilimsel kriterlere uygun bir makale

responsibility to prepare a manuscript that meets scientific criterias.

Statements or opinions expressed in the manuscripts reflect the views of the author(s) and not the opinions of the Medical Faculty of Gaziantep Islam Science and Technology University, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All manuscripts involving a research study must be evaluated in terms of biostatistics and it must be presented altogether with appropriate study design, analysis and results. ***p*** values must be given clearly in the manuscripts. Other than research articles, reviews, case reports, letters to the editor, etc. should also be original and up to date, and the references and, if any, their biostatistical parts should be clear, understandable and satisfactory.

The publication language of the journal is English. In addition, the abstract part of the article must be uploaded in both Turkish and English. Manuscripts should be evaluated by a linguist before being sent to the journal.

All manuscripts and ecorrespondence with the editorial board must be sent to the editorial office, at https://dergipark.org.tr/tr/pub/eams.

According to the Law on Intellectual and Artistic Works, which was first published in the Official Gazette with the law number 5846 on 13/12/1951, whose web address is below, and on which subsequently various changes have been made or novel parts added in time, all kinds of publication rights of the articles accepted for publication belong to the institution that

hazırlamak yazarların sorumluluğundadır.

Dergide yayınlanan yazılarda ifade edilenler veya görüşler, Gaziantep İslam Bilim ve Teknoloji Üniversitesi Tıp Fakültesi, editörler, yayın kurulu ve/veya yayıncının görüşlerini değil, yazar(lar)ın görüşlerini yansıtır; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez.

Araştırma çalışması içeren tüm yazılar biyoistatistiksel açıdan değerlendirilmeli ve uygun çalışma düzeni, verilerin analizi ve sonuçları ile birlikte sunulmalıdır. ***p*** değerleri yazılarda açık olarak verilmelidir. Araştırma makaleleri dışında derlemeler, olgu sunumları, editöre mektuplar vb. de orijinal/özgün ve güncel olmalı ve kaynaklar ile eğer varsa biyoistatistiksel kısımlar açık, anlaşılır ve tatminkâr şekilde açıklanmış olmalıdır.

Derginin yayın dili İngilizce'dir. Ayrıca makalenin özet kısmı hem Türkçe hem de İngilizce olarak yüklenmelidir. Yazılar dergiye gönderilmeden önce bir dilbilimci/konunun uzmanı tarafından değerlendirilmelidir.

Bütün çalışmalar ve editör kurulu ile yazışmalar çevrimiçi olarak, https://dergipark.org.tr/tr/pub/eams adresi üzerinde yayın ofisine gönderilmelidir.

İnternet adresi aşağıda belirtilmiş olan, ilk olarak 13/12/1951 tarih ve 5846 sayılıKanun ile Resmi Gazete'de yayımlanan, sonraları üzerinde değişiklikler yapılmış veya yeni kısımlar eklenmiş olan Fikir ve Sanat Eserleri Kanunu'na göre; yayına kabul edilen makalelerin her türlü yayın hakkı dergiyi yayınlayan kuruma aittir. Ancak makalelerdeki düşünce ve önerilertamamen yazarların sorumluluğundadır.

published the journal. However, the thoughts and suggestions in the articles are entirely the responsibility of the authors.
https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210818145630_406d24df.pdf

https://www.gibtu.edu.tr/Medya/Birim/Dosya/20210818145630_406d24df.pdf

Author Guidelines

Submission of a paper will be taken into consideration provided that it has not previously been published and not being considered at that moment for publication elsewhere. Decision as to publication of papers submitted to the ***Experimental and Applied Medical Science*** will be based on the opinion of the Editorial Board as to the significance and originality of the work.

Manuscripts should be prepared electronically by using “office word” or any other text-processing package compatible with that, formatted for A4 size, double-spaced throughout, and using a “Times New Roman” 12-point font. Articles must be written in English. Abstracts must be written in both Turkish and English. Text should flush left, and not be justified. Words should not be hyphenated. Pagesshould be numbered sequentially.

There should be a separate title page with:

a) The title
b) The authors' names
c) The laboratory of origin, with complete address of each author
d) A running title
e) Corresponding author and e-mail
f) Conflict of interest
g) Acknowledgements

The main body of full-length paper should be divided into:

1. Abstract
2. Introduction
3. Material and Methods
4. Results
5. Discussion

Yazım Kuralları

Bir çalışmanın dergimize gönderilmesi bu çalışmanın daha önce yayınlanmamış veya başka bir akademik dergide şu anda yayınlanmak üzere değerlendirilmiyor olması koşulu ile mümkündür.***Experimental and Applied Medical Science***’a gönderilen her türlü çalışmanın yayınlanmasına ilişkin karar, Yayın Kurulu'nun çalışmanın önemi ve özgünlüğü konusundaki görüşüne dayanacaktır.

Çalışmalar, ya “office word” programı ile ya da bu program ile uyumlu uygun bir metin işleme programı kullanılarak, A4 boyutunda hazırlanmalı, baştan sona çift aralıklı ve “Times New Roman” tarzında 12 punto yazı tipi kullanılarak elektronik ortamda yazılmalıdır. Makaleler İngilizce yazılmalıdır. Özetler hem Türkçe hem de İngilizce olarak yazılmalıdır. Metin iki yana yaslandırılmamalı, sadece sola yaslanmamalıdır. Kelimeler kısa çizgi ile hecelenmemelidir. Sayfalar sırayla numaralandırılmalıdır.

Aşağıdakileri içeren ayrı bir başlık sayfası olmalıdır:

a) Başlık
b) Yazarların isimleri
c) Her yazarın tam adresi ile birlikte çalıştıkları laboratuarlar
d) Kısa başlık
e) İletişimdeki yazar ve iletişim bilgileri
f) Çıkar çatışması beyanı
g) Bilgilendirme

Tam uzunluktaki kağıdın ana gövdesi şu bölümlere ayrılmalıdır:

1. Özet
2. Giriş

6. Conclusion
7. Conflict of interest
8. Acknowledgement
9. References

In general, there are no a maximum specific word length laid down as a condition for any manuscript. The general principle is that a manuscript should be as long as necessary to communicate the scientific message clearly and effectively at the most, but should be as short as possible to avoid undue repetition or redundancy with a complete presentation of the information.
In the *Materials and Methods* section, the source of all compounds, equipment or software should be identified by the full name of the supplier, city, state/country. The chemical names of any drug should precede the trade name.
Papers describing animal experiments must define species, strain, sex, age, supplier and number of animals used. An ethical statement concerning the use of animals, or the details of ethical approvals, consent and recruitment of human subjects should be clearly stated. *Results* and *Discussion* can be broken down into subsections for improving the comprehensibility. The Results should not repeat methodological details and should avoid the discussion of the data.
The results of statistical tests should be incorporated in the body of the text, typically in the *Results* section, rather than in figure legends. Adequate description of statistical analysis should be provided. Statistical measures of variation in the text, illustrations and tables, should be identified.

3. Gereç ve Yöntemler
4. Sonuçlar
5. Tartışma
6. Bağlam
7. Çıkar çatışması
8. Bilgilendirme
9. Kaynaklar

Genel olarak, herhangi çalışma için şart koşulan belirli bir kelime sayısı/metin uzunluğu yoktur. Genel ilke; bir makalenin bilimsel mesajı açık ve etkili bir şekilde iletmek için gerektiği kadar uzunolabileceği, ancak gereksiz tekrar veya fazlalık olmadan bilgilerin eksiksiz birsunumunu elde etmek için mümkün olduğunca kısa olması gerektiğidir.
Gereçler ve Yöntemler bölümünde, tüm bileşiklerin, malzemelerin veya yazılımların kaynağı, tedarikçinin tam adı, şehir, eyalet/ülke ile tanımlanmalıdır. Herhangi bir ilacın kimyasal isimleri ticari isminden önce gelmelidir.
Hayvan deneylerini açıklayan makaleler,tür, soy, cinsiyet, yaş, tedarikçi ve kullanılan hayvan sayısını açıkça tanımlamalıdır. Hayvanların kullanımına ilişkin bir etik beyan veya insan deneklerin etik kurul onayları, bilgilendirilmiş onamları ve çalışmaya dâhil edilmelerine ilişkin ayrıntılar açıkça belirtilmelidir. *Sonuçlar ve Tartışma* bölümleri, anlaşılırlığı artırmak için alt bölümlere ayrılabilir. Sonuçlar, metodolojik ayrıntıları tekrarlamamalı ve verilerin tartışılmasından kaçınmalıdır.
İstatistiksel testlerin sonuçları, şekillerin altındaki açıklama kısımlarından ziyade metnin gövdesine, tipik olarak Sonuçlar bölümüne dâhil edilmelidir. İstatistiksel analizin yeterli bir şekilde açıklaması sağlanmalıdır. Metinde, resimlerde ve

All dimensions and measurements must be specified in the metric system.

All subscripts, superscripts, Greek letters and unusual characters must be clearly identified.

In the text, abbreviations should be used consistently. Abbreviations should be defined on first use.

References should be designed in “Vancouver” style. While writing references, “Times New Roman” 10 point font should be used. Multiple authors should be separated by a comma. If there are more than three authors, after the 3rd author, "et al." should be inserted with a comma, for both article and book references. If reference is made from a chapter in a book and there are many authors belonging only to this chapter, the title and chapter of the book are indicated, the first three of the chapter authors are written, and "et al." statement is added for subsequent authors.

Example:

1. Perell KL, Nelson A, Goldman RL, et al. Fall risk assessment measures: an analytic review. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(12):M761-6.
2. Ha H, Han C, Kim B. Can Obesity Cause Depression? A Pseudo-panel Analysis. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2017;50(4):262-7.
3. Çekmen MB, Turgut M, Türköz Y, etal. Nitrik Oksit (NO) ve Nitrik Oksit Sentaz (NOS)'ınFizyolojik ve Patolojik Özellikleri. Türkiye Klinikleri Journal of Pediatrics. 2001;10(4):226-35.
4. Parlakpınar H, Örüm MH, Acet A. Kafeik

tablolarda istatistiksel varyasyon ölçütleri tanımlanmalıdır.

Tüm boyutlar ve ölçüler metrik sistemde belirtilmelidir.

Tüm alt simgeler, üst simgeler, Yunan harfleri ve olağandışı karakterler açıkça tanımlanmalıdır.

Metinde kısaltmalar tutarlı bir şekilde kullanılmalıdır. Kısaltmalar ilk kullanımda tanımlanmalıdır.

Kaynaklar “Vancouver” tarzında yazılmalıdır. Kaynaklar yazılırken, “Times New Roman” 10 punto kullanılmalıdır. Birden çok yazar virgülle ayrılmalıdır. Hem makale hem de kitap referanslarında, eğer üçten çok yazar varsa, 3. Yazardan sonra virgül ve “et al.” ifadesi kullanılmalıdır. Kitapta bir bölümden referans yapılıyorsa ve sadece bu bölüme ait çok sayıda yazar varsa, kitabın başlığı ve bölümü belirtilip, bölüm yazarlarının ilk üçü yazılıp veardından sonraki yazarlar için “et al.” ifadesi eklenmelidir.

Örnek:

1. Perell KL, Nelson A, Goldman RL, et al. Fall risk assessment measures: an analytic review. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(12):M761-6.
2. Ha H, Han C, Kim B. Can Obesity Cause Depression? A Pseudo-panel Analysis. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2017;50(4):262-7.
3. Çekmen MB, Turgut M, Türköz Y, etal. Nitrik Oksit (NO) ve Nitrik Oksit Sentaz (NOS)'ınFizyolojik ve Patolojik Özellikleri. Türkiye Klinikleri Journal of Pediatrics. 2001;10(4):226-35.

asit fenetil ester (KAFE) ve miyokardiyal iskemi reperfüzyon (Mİ/R) hasarı. İnönü Üniversitesi Sağlık Bilimleri Dergisi 2012; 1: 10-5.

5. Yıldırım AB. The effects of maternal hypothyroidism on the immunoreactivity of cytochrome p450 aromatase in the postnatal rat testes. 2015; Doctoral thesis.

6. https://hsgm.saglik.gov.tr/depo/birimler/kanserdb/istatistik/Trkiye_Kanser_statistikleri_2016.pdf (Last access date: 21.09.2020).

7. Kuran O, İstanbul, Filiz Kitabevi. Sistematik Anatomi. 1983 p. 76-9.

8. Abbas AK, Andrew H Lichtman, Shiv Pillai. Cellular and Molecular Immunology. 6th ed. Philadelphia: Saunders Elsevier; 2007 p. 121-56.

Submit illustrations as separate files, only as TIFF or EPS files, with a minimum resolution of 300dpi.

Tables of numerical data should each be typed with double spacing on separate pages numbered in sequence in numerals, provided with a heading, and referred to in the text, as Table 1, Table 2, etc. Each table should have a brief but descriptive heading. Explanatory matter should be included in footnotes to the table.

We accept electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, movies, animation sequences, high-resolution images, background datasets, sound clips and more.

Disclosure of conflict of interest and

4. Parlakpınar H, Örüm MH, Acet A. Kafeik asit fenetil ester (KAFE) ve miyokardiyal iskemi reperfüzyon (Mİ/R) hasarı. İnönü Üniversitesi Sağlık Bilimleri Dergisi 2012; 1: 10-5.

5. Yıldırım AB. The effects of maternal hypothyroidism on the immunoreactivity of cytochrome p450 aromatase in the postnatal rat testes. 2015; Doctoral thesis.

6. https://hsgm.saglik.gov.tr/depo/birimler/kanserdb/istatistik/Trkiye_Kanser_statistikleri_2016.pdf (Last access date: 21.09.2020).

financial support is required at the time of

7. Kuran O, İstanbul, FilizKitabevi. Sistematik Anatomi. 1983 p. 76-9.
8. Abbas AK, Andrew H Lichtman, Shiv Pillai. Cellular and Molecular Immunology. 6th ed. Philadelphia: Saunders Elsevier; 2007 p. 121-56.

Görseller, minimum 300 dpi çözünürlükte, yalnızca TIFF veya EPS dosyaları halinde ve ayrı dosyalar olarak gönderilmelidir.

Sayısal veri tablolarının her biri, sayılarla sırayla numaralandırılmış bir başlık ile birlikte ve metinde Tablo 1, Tablo 2, vb. olarak atıfta bulunulmuş halde, ayrı sayfalarda çift aralıkla hazırlanmalıdır. Her tablonun kısa ama açıklayıcı bir başlığı olmalıdır. Tablo dipnotlarında açıklayıcı hususlara yer verilmelidir.

Bilimsel araştırmalarınızı desteklemek ve geliştirmek için elektronik ek materyaller kabul edilmektedir. Ek dosyalar, yazara, destekleyici uygulamaları, filmleri, animasyon dizilerini, yüksek çözünürlüklü görüntüleri, arka plan veri kümelerini, ses kayıtlarını ve daha fazlasını yayınlamak için ek olanaklar sunmaktadır.

Başvuru sırasında çıkar çatışmasının ve mali

submission. The authors are responsible for informing the Journal of any additional conflicts of interest or financial support that may arise prior to the date of publication of their paper. All authors must individually disclose all potential conflicts of interest and financial support, whether or not directly related to the subject of their paper.

destek konularının açıklanması elzemdir. Yazarlar, makalelerinin yayımlanma tarihinden önce ortaya çıkabilecek ek çıkar çatışmalarını veya bulunan mali destekleri dergiye bildirmekle yükümlüdür. Tüm yazarlar, makalelerinin konusuyla doğrudan ilgili olsun ya da olmasın, tüm olası çıkar çatışmalarını ve mali desteği bireysel olarak açıklamalıdır.

Editorial Board/Editör Kurulu

İbrahim Halil Türkbeyler, Assoc. Prof.
Dr. Ersin Arslan Training and Research Hospital, Geriatrics Department
ihturkbeyler@gmail.com
Ayşegül Burçin Yıldırım, Asst. Prof.
Gaziantep Islam, Science and Technology University, Medical Faculty, Medical Histology and Embryology Department
abyildirim@gibtu.edu.tr

İbrahim Halil Türkbeyler, Assoc. Prof.
Dr. Ersin Arslan Training and Research Hospital, Department of Internal Medicine, Division of Geriatrics
ihturkbeyler@gmail.com
Ayşegül Burçin Yıldırım, Asst. Prof.
Gaziantep Islam, Science and Technology University, Medical Faculty, Medical Histology and Embryology Department
abyildirim@gibtu.edu.tr
Mehmet Göl, Asst. Prof.
Gaziantep Islam Science and Technology University, Medical Faculty, Medical Physiology Department
mehmet.gol@gibtu.edu.tr
İbrahim Halil Kenger, Asst. Prof.
Gaziantep Islam Science and Technology University, Medical Faculty, Medical Genetics Department
ibrahimhalil.kenger@gibtu.edu.tr
Leyla Çimen, Asst. Prof.
Gaziantep Islam Science and Technology University, Medical Faculty, Medical Biochemistry Department
leyla.cimen@gibtu.edu.tr
Hikmet Dinç, Assoc. Prof.
Gaziantep Islam Science and Technology University, Medical Faculty, Medical Pharmacology Department
hikmet.dinc@gibtu.edu.tr
Rabia Taşdemir, Asst. Prof.
Gaziantep Islam Science and Technology University, Medical Faculty, Department of Anatomy
rabia.tasdemir@gibtu.edu.tr
Cuneyd Parlayan, Asst. Prof.
Bahçeşehir University, Medical Faculty, Bioistatistics and Medical Informatics Department
cparlayan@medipol.edu.tr
Masa-Aki Ikeda
Tokyo Medical and Dental University, Garduate School of Medical and Dental Science
mikeda.emb@tmd.ac.jp
Maizaton Atmadini Abdullah
University of Putra Malaysia, Senior Medical Pathology Lecturer
maizaton@upm.edu.my
Abu Shameem Md Saadat Khandakar
Gaziantep University, Medical Faculty, Medical Biology Department
shameemsaadat@gantep.edu.tr

Selcen Çakır
selcencakir@gmail.com
Serdar Özdemir
dr.serdar55@hotmail.com
Çağla Yiğitbaş
caglayigitbas@hotmail.com
Özlem Akay
ozlem.akay@gibtu.edu.tr
İbrahim Halil Kenger
ibrahimhalil.kenger@gibtu.edu.tr

Contents/İçindekiler

365 **Other Mediators At Age-Related Macular Degeneration**

Burak TURGUT, Hakika ERDOGAN, Nevin ILHAN, Ismail ERSAN

372 **A Case of Urinary System Infection Requiring Hospitalization: Emphysematous Cystitis**

Fulya KOSE, Hatice Seyma AKCA, Dilek ATIK

376 **Is The Level Of Knowledge Of Healthcare Workers About Hepatitis A, B, C Transmission Routes Sufficient?**

Safiye KOCULU DEMIR, Ozgur ONAL, Hakan KUTLU, Adem ALBAYRAK, Zuhal YESILBAG

387 **The Effect of Nursing and Midwifery Students Attitudes Toward Information and Communication Technologies on Their Readiness for Mobile Learning**

Aliye BULUT, Sema İCEL, Zehra CERCER

400 **Sectionary Analysis Of Thyroid Function Tests, Vitamin B12 And Folic Acid Levels In Patients With Type 2 Diabetes Mellitus, Hypertension, Chronic Renal Disease And Gastroesophageal Reflux Disease**

Hamit YILDIZ, Deniz YILDIZ PEHLİVAN

409 **May Neutrophil Lymphocyte Ratio Be A Predictor of Neuropathy in Diabetic Patients?**

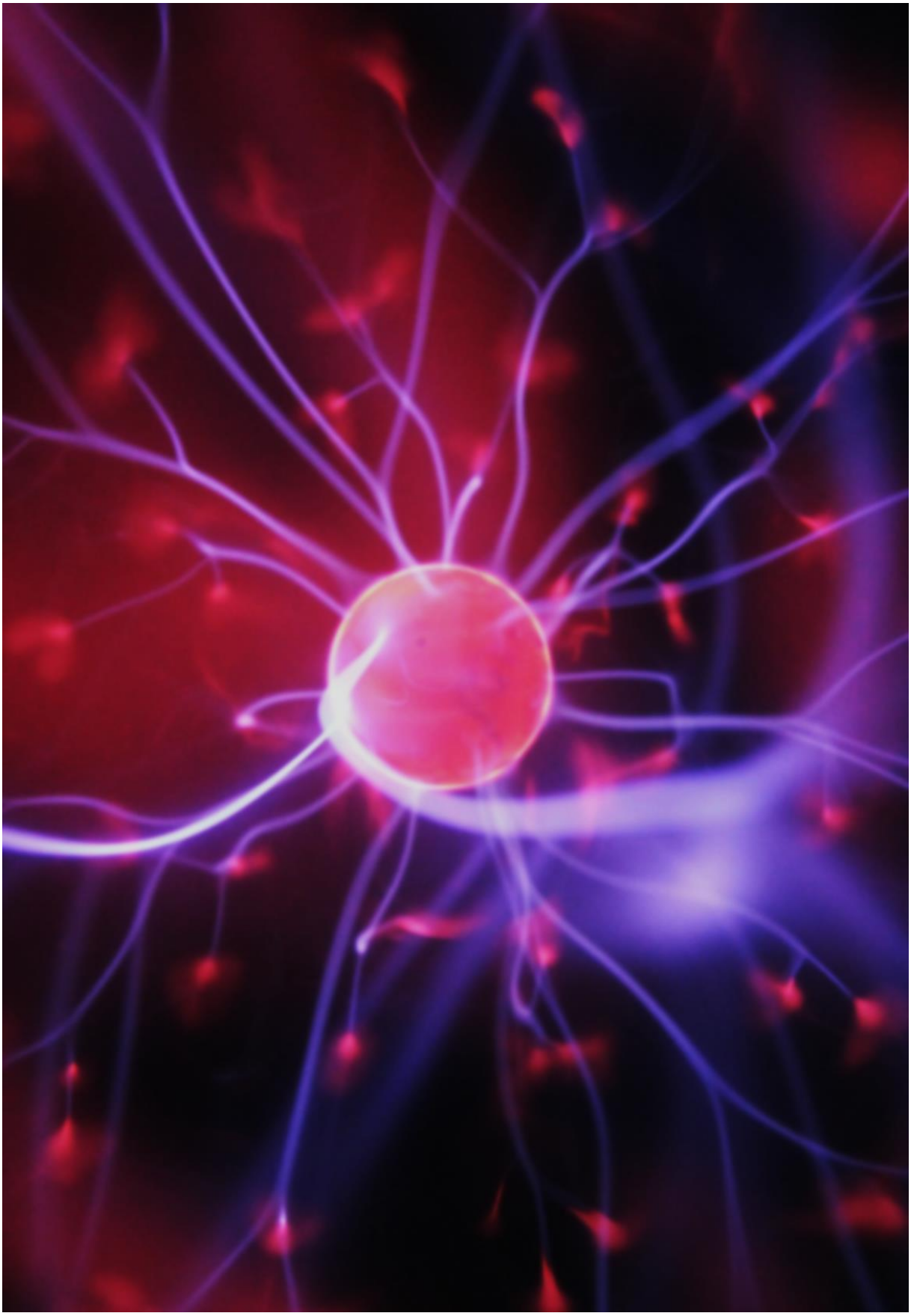
Hamit YILDIZ, Deniz YILDIZ PEHLİVAN

419 **SARS-CoV-2 Infections in Vaccinated vs Unvaccinated Healthcare Workers: Assessment of the Effectiveness of CoronaVac**

Hadiye DEMIRBAKAN, İPEK KOCER, Aysen BAYRAM

430 **Leptin and Metabolic Effects**

Feride KOCA, Leyla CIMEN



Experimental and Applied Medical Science, 3,3: 365-370, 2022. DOI 10.46871/eams.2022.41

Other Mediators At Age-Related Macular Degeneration

Burak TURGUT[1], Hakika ERDOGAN[1], Nevin ILHAN[2], Ismail ERSAN[1]
[1]*Canakkale Onsekiz Mart University, Faculty of Medicine, Opthalmology Department,*
[2]*Firat University, Faculty of Medicine, Biochemistry Department*

Abstract

Objective: *In some patients, even if anti-VEGF therapy is repeatedly administered at certain intervals, no response is obtained. Therefore, a search for new treatment methods has arisen. The aim of this study was to investigate the relevance of mediators such as Erythropoietin, Interleukin 17, and* Angiotensin2*, which are all involved in proliferation, apoptosis, oxidative stress, and inflammation in age-related macular degeneration.*

Metods: *EPO, IL-17, and Angiotensin 2 levels were evaluated by examining the blood samples of patients who did not have any systemic disease or chronic eye disease except Age-related Macular Degeneration (AMD).*

Results: *The patients were divided into 3 groups. Groups 1,2, and 3 were determined as the control group, dry type group, and neovascular type group respectively. For the purpose of this study, erythropoietin, interleukin 17,* angiotensin2 *were examined in the blood samples of patients. As a result of the analyses, a statistically significant difference was detected between the groups in terms of EPO, IL-17, and Angiotensin 2.*

Conclusion: *If the relationship between many factors related to age-related macular degeneration can be clearly defined, the perspective on treatment may change, especially in treatment-resistant patients.*

Keywords: *Age-related Macular Degeneration, Erythropoietin, Interleukin 17,* Angiotensin 2

***Corresponding author:** Hakika Erdogan, e-mail: hakika.erdogan@comu.edu.tr, ORCID ID: 0000-0001-7749-2814.

Introduction

AMD accounts for 6-9% of legal blindness (1). The disease is divided into two types: Dry type (DT) and neovascular type (NVT). In both the DT and NVT, the main causes are the deterioration in retinal pigment epithelium (RPE), which is triggered by apoptosis, oxidative stress, carbonyl stress, and inflammation. It is estimated that approximately 288 million people will have the disease by 2040, and 15 million of these patients will have the NVT in 2050. Despite the high morbidity of the disease, treatment options and preventive factors are limited. (1-6) In fact, although a complete cure cannot be achieved, anti-inflammatory drug treatment, anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection, and nutritional therapy are commonly used for treatment. (4, 5) In the NVT, for which the prognosis is the worst, anti-VEGF preparations are administered intravitreally. Treatment is scheduled monthly or includes regimens that can be repeated as needed. Even with such a strict treatment protocol, response is observed only in one third of the patients. (2)

The use of mediators that play an important role in inflammation and apoptosis in inflammatory diseases such as AMD is a controversial issue. Mediators such as EPO, IL-17, Ang-2 have been studied in many inflammatory diseases and found to be relevant. (7-10) If the relationship of these mediators with AMD can be clearly identified, it can be tested in patients unresponsive to anti-VEGF therapy.

The aim of our study was to determine the relationship between the AMD and consisting of Erythropoietin (EPO), Interleukin 17 (IL-17), Angiotensin2 (Ang-2), previously studied as regards inflammatory diseases.

Subjects and Methods

Late-stage, symptomatic patients diagnosed with AMD who applied to the university retina outpatient clinic were examined in this prospective study. (11) The patients with systemic diseases (diabetes, hypertension, thyroid, rheumatological disorders and cancer, etc.) and concomitant chronic eye diseases (uveitis, glaucoma, vaso-occlusive disorders), and those who had received intraocular injections, as well as those with a BMI within the obesity range were excluded from the study. Of all the patients, 14 of them (Group 1) with DT AMD and 18 (Group 2) of them with the NVT AMD were included in the study. For the control group, 14 participants with the same inclusion criteria were included in the study (Group 3).

Blood samples were collected from patients and health checks doneto measure the EPO, IL- 17, Ang-2levels at 9 am after overnight fasting in all subjects.

All subjects rested for 15 min before the blood collection process. The samples were delivered to the laboratory within 20 min. and centrifuged in 2000 rpm for 10 min at 4°C. Thesera were stored at −80°C until the bio-chemical assay was performed. For serum Human Salusin-β, EPO, IL-17, Ang-2 measurements, a commercial kit (Sunred Bio, Baoshan, Shanghai) was used. Serum salusin-β, EPO, IL-17, Ang-2 levels were assayed by enzyme- linked immunosorbent test (ELISA), following the manufacturer's instructions. The minimum detectable

level (sensitivity) was less than 0.157 ng/mL and the assay range for EPO, IL-17, Ang-2 was 0.2–60 ng/mL. Intra- and inter-assay CVs were less than 10% and 12%, respectively. All samples were measured spectrophotometrically using ELx-800TM Absorbance Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA) at 450 nm. The biochemist blindly assayed samples. The results are presented as ng/ml.

The study was conducted in full accordance with the Declaration of Helsinki and approved by the Ethics Committee of the university (Date: 30.03.2017, Number: 16). All the study subjects were provided with an informed consent.

The data obtained from the patients were transferred to SPSS. “Shapiro-Wilk Test” was used to detect whether the data ofEPO, IL-17, Ang-2” (ng/ml) in the control group, NVT and DT groups separately showed a normal distribution. Comparison analyses were calculated by Kruskal-Wallis Test and correlation analyses were calculated with Spearman-Brown correlation coefficient.

Results

This study included a total of 46 participants, 14 of whom were healthy, whereas32 of them had AMD. The age range of the patients in the groups were 76.35 ± 8.13 years, 77.32±7.15 years, and 77.27±7.80 years for the DT group, NVT group and the control group, respectively. There were 8 male and 6 female participants in the DT, 8 male and 10 female participants in the NVT, and 7 male and 7 female participants in the control group. No statistically significant difference was found between the groups in terms of age and gender ($p>0.05$).However, there was a statistically significant difference between the groups in terms of the EPO, IL-17 and Ang-2.The DT group had the highest values of EPO and the control group had the highest value of IL-17. The highest Ang-2 value was found in the NVT group. The mediators examined in the patients are shown in Table 1.

Table 1. Molecular levels in blood

Mediators	Group	N	Value (ng/ml)	P
EPO	Control	14	234.57±57.98	0.0001
	Dry type	14	1109.07±691.32	
	Neovascular type	18	689.09±730.97	
IL-17	Control	14	304.56±278.77	0.0001
	Dry type	14	89.71±30.81	
	Neovascular type	18	80.1±18.97	
Ang-2	Control	14	7272.62±1531.08	0.001
	Dry type	14	10013.27±1842.66	
	Neovascular type	18	11634.31±36667.86	

N, number of the participants; Erythropoietin, EPO; Interleukin 17, IL-17; *Angiotensin2,* Ang-2

EPO is a glycoprotein hormone, which plays a critical role as antiapoptotic, antioxidant, angiogenic, anti-inflammatory, neuroprotective and stem cell protector in proliferation, differentiation, and apoptosis mechanisms. (12) Its main mechanism of action is the hematopoietic system, but its secretion is increased secondary to hypoxia in many organs. In the eye, both its receptor and EPO have been shown in photoreceptor cells, ganglion cells, inner nuclear layer, retinal pigment cells and choroid.(13,14) EPO levels are higher in the RPE than in plasma.(13)It is claimed in some studies that an EPO level is elevated in many eye diseases to the extent that it creates a protective effect, while some studies argue the opposite.(7) One study, for example, showed that EPO could affect the progression of diabetic retinopathy positively, while another reported that it negatively affected the prognosis.(7, 15, 16) In fact, the stages of diabetic retinopathy are different in each study. While it was observed to be protective in the early stage, it aggravated the worsening in the late stage. Further studies are needed to show whether EPO levels change as to disease and its stages. In the current study, the lowest EPO level was found in the control group, while the highest level was found in the DT AMD group. Whether elevated EPO levels are a protective mechanism from NVT AMD should be investigated with new studies.

IL-17 is a cytokine, which is produced by helper 17 cells. (17) It has been studied in serum and cell cultures of patients with the AMD. Three different values have been observed: a value with no statistical difference from to the control group, and that of a greater level and a lower level.IL-17 level was found to be lower especially in treatment-resistant groups. (18-23) In the current study, IL-17 levels were the lowest in the group with the NVT. It is quite interesting that IL-17 levels were variable. Observing low levels in treatment-resistant patients is especially a controversial issue. Whether or not IL-17 levels show a genetic pattern is one of the subjects to be investigated. In such a case, the perspective on treatment may change completely. For this, it may be appropriate to compare the results of a multicentre study.

Ang-2 is a hormone that is important for blood pressure regulation. Ang-2 and renin angiotensin system are known to reside in the RPE.(24) Another widely-known issue is that Ang-2 increases the production of extracellular matrix while

disrupting the RPE barrier.(25- 27) In this connection, some studies have shown the relationship between angiotensin activity and the choroidal neovascular membrane.(28)Another study argued that the activity of the angiotensin 1 receptor is associated with the activation of VEGF, which is a risk factor for AMD.(29)This was supported by the current study, in which the highest Ang-2 level was found in NVT AMD.

AMD degeneration formation and treatment mechanisms have not been fully elucidated. There is currently no effective treatment method. While vitamin supplements are recommended for patients with the DT, intravitreal VEGF is actively used for those with the NVT. The response is good in some patients, but the others turn out to be resistant to treatment, leading to the search for new treatment models. In the current study, blood levels of various agents involved in proliferation, apoptosis, oxidative stress, and inflammation related to the eye were examined. The levels of these agents had been studied for different diseases before, but the values were observed differently in each study. No clear conclusions could be drawn from the studies because of the differences in patients' samples, countries, diseases, stages of the diseases, and ages. In many studies, as is the case in the current study, the number of participants seems to be small. This is the most important limiting factor in the current study and the others. However, the common feature of the studies is that these molecules affect the pathogenesis of the disease in direct or indirect ways. In order to determine the effects of these molecules, future studies are needed with multifocal, similar, and larger groups. It has not been clarified whether these molecules are protective or aggravating. However, the increase in the number of such studies may change the perspective for AMD.

Conclusion

As a result, other mediators besides the VEGF may play an active role in AMD. Understanding the roles of the molecules will make positive contributions to treatment efficacy.

Conflicts of Interest

Turgut B, None; Erdogan H, None; Ilhan N, None; Ersan I, None

Acknowledgements

Foundations : Turgut B, None; Erdogan H, None; Ilhan N, None; Ersan I, None

References

1. Fleckenstein M, Keenan TDL, Guymer RH et.all. Age-related macular degeneration. Nature Reviews Disease Primer 2021; 7(1): 31. doi: 10.1038/s41572-021-00265-2.
2. Mettu, P.S., M.J. Allingham, S.W. Cousins. Incomplete response to Anti-VEGF therapy in neovascular AMD: Exploring disease mechanisms and therapeutic opportunities. Progress in Retinal and Eye Research 2021; May; 82:100906. doi: 10.1016/j.preteyeres.2020.100906
3. Iglicki M, David Pérez González DP, Loewenstein A et al. Longer-acting treatments for neovascular age-related macular degeneration—present and future. Eye 2021; 35(4): 1111-1116. doi: 10.1038/s41433-020-01309-9
4. Cho YK Dae-Hun, Park DH, Jeon IC. Medication Trends for Age-Related Macular Degeneration. International journal of molecular sciences 2021; 22(21): 11837. doi: 10.3390/ijms222111837
5. Lin JB, Omar Halawa OA, Husain D et al. Dyslipidemia in age-related macular degeneration. Eye 2022; Feb;36(2): 312-318. doi: 10.1038/s41433-021-01780-y
6. Armento A, Ueffing M, and S.J. Clark. The complement system in age-related macular degeneration. Cellular and molecular life sciences : CMLS 2021; 78(10): 4487-4505. doi: 10.1007/s00018-021- 03796-9
7. Feizi S, Ansari MA, Karimian F et al. Use of erythropoietin in ophthalmology: a review. Surv Ophthalmol 2022; Mar-Apr;67(2): 427-439 doi: 10.1016/j.survophthal.2021.06.002
8. Güler M, Aydın S, Urfalıoğlu S et al. Aqueous humor heat-shock protein 70, periostin, and irisin levels in patients with pseudoexfoliation syndrome. Arq Bras Oftalmol 2020; 83(5):378-382. doi: 10.5935/0004-2749.20200046
9. Wang H, Zhang M, Zhou H et al. Salusin-β Mediates High Glucose-Induced Inflammation and Apoptosis in Retinal Capillary Endothelial Cells via a ROS-Dependent Pathway in Diabetic Retinopathy. Diabetes Metab Syndr Obes 2021; 14: 2291-2308. doi:10.2147/DMSO.S301157
10. Biswal MR, Wang Z, Paulson RJ et al. Erythropoietin Gene Therapy Delays Retinal Degeneration Resulting from Oxidative Stress in the Retinal Pigment Epithelium. Antioxidants (Basel, Switzerland) 2021; 10(6): 842. doi: 10.3390/antiox10060842
11. Thomas CJ, Mirza RG , Gill MK. Age-Related Macular Degeneration. Med Clin North Am 2021; 105(3):473-491. doi: 10.1016/j.mcna.2021.01.003
12. Girolamo F, Coppola C, Ribatti D et al. Angiogenesis in multiple sclerosis and experimental autoimmune encephalomyelitis. Acta neuropathologica communications 2014; 2(1):1-17. doi: 10.1186/s40478-014-0084-z.
13. Rex TS, Allocca M, Domenici L et al. Systemic but not intraocular Epo gene transfer protects the retina from light-and genetic-induced degeneration. Molecular Therapy. 2004; 10(5):855-861. doi: 10.1016/j.ymthe.2004.07.027
14. Caprara C, Britschgi C, Samardzija M et al. The erythropoietin receptor is not required for the development, function, and aging of rods and cells in the retinal periphery. Molecular Vision 2014; 20:307.
15. Rex TS, Kasmala L, Bond WS et al. Erythropoietin slows photoreceptor cell death in a mouse model of autosomal dominant retinitis pigmentosa. PLoS One 2016; 11(6): e0157411. doi: 10.1371/journal.pone.0157411.
16. Rex TS, Wong Y, Kodali K et al. Neuroprotection of photoreceptors by direct delivery of erythropoietin to the retina of the retinal degeneration slow mouse. Experimental Eye Research 2009; 89(5): 735-740. doi: 10.1016/j.exer.2009.06.017.
17. Li Y, Zhou Y. Interleukin-17: The Role for Pathological Angiogenesis in Ocular Neovascular Diseases. The Tohoku Journal of Experimental Medicine 2019; 247(2): 87-98. doi: 10.1620/tjem.247.87
18. Pongsachareonnont P, Mak MYK, Hurst CP et al. Neovascular age-related macular degeneration: intraocular inflammatory cytokines in the poor responder to ranibizumab treatment. Clinical ophthalmology (Auckland, N.Z.)

2018; 12: 1877-1885. 10.2147/OPTH.S171636.

19. Singh A, Subhi Y, Krogh Nielsen M et al. Systemic frequencies of T helper 1 and T helper 17 cells in patients with age-related macular degeneration: A case-control study. Scientific Reports 2017; 7: 1-9. doi: 10.1038/s41598-017-00741-4
20. Wu Q, Liu B, Yuan L et al. Dysregulations of follicular helper T cells through IL-21 pathway in age- related macular degeneration. Molecular Immunology 2019; 114: 243-250. doi: 10.1016/j.molimm.2019.07.028
21. Nassar K, Grisanti S, Elfar E et al. Serum cytokines as biomarkers for age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2015; 253(5): 699-704. doi: 10.1007/s00417-014- 2738-8.
22. Chen J, Wang W, Li Q. Increased Th1/Th17 Responses Contribute to Low-Grade Inflammation in Age- Related Macular Degeneration. Cell Physiol Biochem. 2017; 44(1): 357-367. doi: 10.1159/000484907
23. Shin JI, Bayry J. A role for IL-17 in age-related macular degeneration. Nat Rev Immunol 2013; 13(9): 701. doi: 10.1038/nri3459-c1
24. Wheeler-Schilling TH, Kohler K, Sautter M et al. Angiotensin II receptor subtype gene expression and cellular localization in the retina and non-neuronal ocular tissues of the rat. European Journal of Neurosciencen 1999;11(10): 3387-3394. doi: 10.1046/j.1460-9568.1999.00787.x.
25. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. Pharmacological reviews 2000; 52(1): 11-34.
26. Praddaude F, Cousins SW, Pêcher C et al. Angiotensin II-induced hypertension regulates AT1 receptor subtypes and extracellular matrix turnover in mouse retinal pigment epithelium. Experimental eye research 2009; 89(1):p. 109-118. doi: 10.1016/j.exer.2009.02.020
27. Pons M, Cousins SW, Alcazar O et al. Angiotensin II-induced MMP-2 activity and MMP-14 and basigin protein expression are mediated via the angiotensin II receptor type 1-mitogen-activated protein kinase 1 pathway in retinal pigment epithelium: implications for age-related macular degeneration.The American journal of pathology 2011; 178(6): 2665-2681. doi: 10.1016/j.ajpath.2011.02.006
28. Nagai N, Oike Y, Izumi-Nagai K et al. Angiotensin II Type 1 Receptor–Mediated Inflammation Is Required for Choroidal Neovascularization. Arterioscler Thromb Vasc Biol 2006; 26: 2252-2259. doi: 10.1161/01.ATV.0000240050.15321.fe
29. Choudhary R, Kapoor MS, Singh A et al. Therapeutic targets of renin-angiotensin system in ocular disorders. Journal of current ophthalmology 2016; 29(1): 7-16. doi: 10.1016/j.joco.2016.09.009.

Experimental and Applied Medical Science, 3,3: 371-374, 2022. DOI 10.46871/eams.2022.42

A Case of Urinary System Infection Requiring Hospitalization: Emphysematous Cystitis

Fulya Kose[1], Hatice Seyma Akca[1], Dilek Atik[1]

[1] University of Karamanoğlu Mehmet Bey, Karaman Education and Research Hospital, Department of Emergency Medicine, Karaman, Turkey.

Abstract

Introduction: *This study describes the clinical course of a patient with type 2 diabetes mellitus and obesity who was diagnosed with a rare emphysematous cystitis; early and effective treatment prevented the development of sepsis and mortality.*

Case Report: *A 52-year-old female patient presented to the emergency department with complaints of fever and pain in the inguinal region. The patient had known hypertension, DM, and obesity. A physical examination revealed tenderness and defense in the right and left lower quadrants of the abdomen. Other system examinations were normal. Laboratory analyses revealed the following: CRP (C-reactive protein) 439 mg/dl, glucose 343 mg/dl, urea 95.9 mg/dl, creatinine 2.11 mg/dl; alanine aminotransferase and aspartate aminotransferase values were within normal limits. In the abdominal tomography air density was observed in the bladder lumen. She was admitted to the infectious diseases clinic with a preliminary diagnosis of urinary system infection. Hydration therapy was started 1 hour after admission to emergency department. Piperacillin tazobactam and ceftriaxone treatment was started. After 12 days of hospitalization, the patient was discharged, whose symptoms regressed without complications.*

Conclusion*: When evaluating urinary system infections in diabetic patients, EC should be included in the differential diagnosis. With hospitalization and effective treatment, the disease can be treated before it progresses to sepsis.*

Key words: *Emphysematous cystitis, urinary system infection, diabetes mellitus*

***Corresponding author:** Hatice Seyma Akca. e-mail: haticeseymaakca@gmail.com. ORCID ID: 0000-0003-2823-9577.

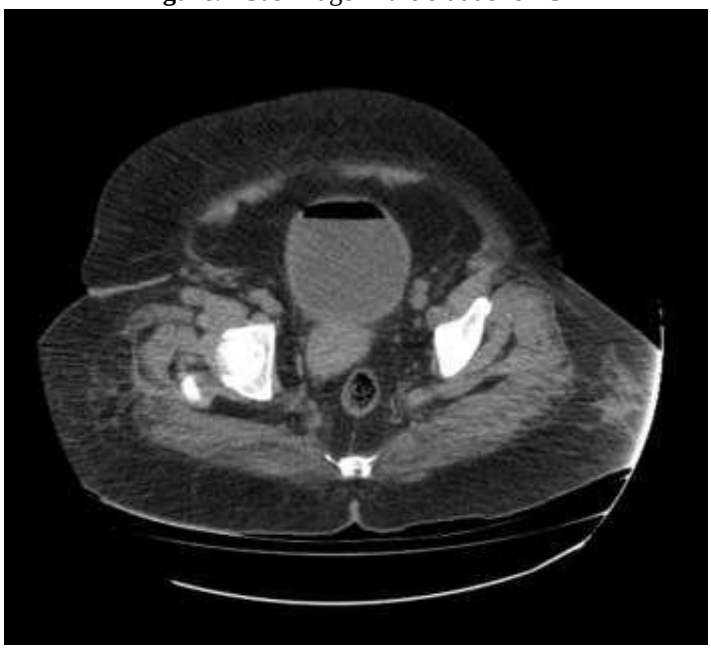
Introduction

Emphysematous cystitis (EC) is characterized by air accumulation in the bladder wall or lumen; it can be seen after urological interventional procedures and, more frequently, in patients with advanced age and diabetes mellitus (DM) (1). Early treatment is necessary to prevent the development of sepsis. This study describes the clinical course of a patient with type 2 DM and obesity who was diagnosed with a rare EC; early and effective treatment prevented the development of sepsis and mortality.

Case Report

A 52-year-old female patient presented to the emergency department with complaints of fever and pain in the inguinal region. The patient had known hypertension, DM, and obesity. She used insulin for DM and beta-blockers for hypertension. A physical examination revealed tenderness and defense in the right and left lower quadrants of the abdomen. Other system examinations were normal. The patient's temperature was 37°, her pulse was 85/min, her respiratory rate was 17/min, and her Ta was 140/80 mmHg. Laboratory analyses revealed the following: hemoglobin 12.3 g/dl, hematocrit 37.1%, white blood cell 6.79 K/µL, CRP (C- reactive protein) 439 mg/dl, platelet 102 K/µL, glucose 343 mg/dl, urea 95.9 mg/dl, creatinine 2.11 mg/dl, sodium:130.3 mmol/L, and potassium: 4.31 mmol/L; alanine aminotransferase and aspartate aminotransferase values were within normal limits. In the patient with HbA1c 14, an examination of centrifuged urine at 40x objective magnification with full urinalysis revealed that the number of erythrocytes in each area was 2,120, and the number of leukocytes was 443. A contrast-enhanced abdominal CT was requested due to the presence of defense in the examination and the fact that the patient was obese. Although intraabdominal air or loculated or diffuse free fluid collection was not observed in the abdominal CT, air density was observed in the bladder lumen (figure.1).

Figure.1 Gas image in the bladder on CT



Intravenous fluid and insulin therapy were started. 500 cc to 2000 cc isotonic 0.9% sodium chloride treatment was given per hour. 300 U of insulin was administered subcutaneously. She was admitted to the infectious diseases clinic with a preliminary diagnosis of urinary system infection. Piperacillin tazobactam treatment was started, and the patient responded positively to the treatment with a decrease in infection parameters. Intravenous ceftriaxone 2x1 treatment was started due to sensitive *E. coli* growth in the patient's urine and blood cultures. The patient was discharged with recommendations (The patient was informed to apply in case of fever, abdominal pain, nausea, vomiting, and pain in the inguinal region.) on the 12th day of hospitalization, with improvement in the clinical findings, an absence of fever, and a decrease in urea and creatinine values. It was observed that the patient did not have any active complaints at the outpatient clinic appointment 1 month later for control purposes, and there were no findings suggestive of reinfection in the laboratory examinations.

Discussion

Although emphysematous cystitis can be seen with nonspecific symptoms such as fever and myalgia, there may be hospital admissions with symptoms such as pain in the inguinal region and sepsis. When kidney and perirenal necrosis develops, it causes mortality over 20%. (2,3) *Escherichia coli* (60%) and *Klebsiella pneumoniae* (10-20%) are the most common agents of emphysematous cystitis, while *Enterobacter aerogenes*, *Proteus mirabilis* and Streptococcus sp. are among the rare agents. *Pseudomonas aeruginosa, Candida albicans, Clostridium perfringens, Enterococcus faecalis, Staphylococcus aureus, Clostridium welchii* have been reported as case reports (4,5). Although a case report of EC due to *Streptococcus salivarius* has been reported (6), *E. coli* is the most common agent in urine culture in EC, and *E. coli* was also found in our case, confirming our preliminary diagnosis (1,7).

In a retrospective study comparing EC with acute cystitis, patients with diabetes, chronic renal failure, and neurogenic bladder were found to have a significantly higher rate of EC diseases than acute cystitis diseases. HbA1c was also observed to be significantly higher in EC. The risk of developing sepsis and mortality is also higher in EC than in acute cystitis (2). In this case, our patient had uncontrolled diabetes. There was no history of urinary catheterization or any interventional procedure. Computed tomography was accepted as the most appropriate diagnostic option. Unlike the patients mentioned in previous studies, our patient had significant obesity. We think that obesity may cause difficulties in the regulation of blood glucose, and thus EC occurs. Ultrasonography was not considered appropriate because of our patient's obesity. Although no bladder catheter was applied during tomography scan, the presence of air in the bladder lumen was also a finding in favor of EC.

EC may also develop due to drugs used by a patient. In a patient with grade 4 chronic renal failure, emphysematous pyelonephritis developed after the administration of suspired, a dopaminergic drug, more than the renal dose (8). Although our patient did not use any drug above the renal dose, we learned that the patient was not compliant with

her insulin therapy.

In addition, in a previous study by Obeidat et al., EC was diagnosed with the presence of gas in the inferior vena cava, and it was reported that the coincidental gas shadows on the great vessel wall should be examined for possible infection (9). The literature also reports a case of EC that was found incidentally in an immunosuppressed patient with pneumomediastinum (10).

Although EC is rare compared to acute cystitis or other urinary infections, it is a disease that requires early treatment. Antibiotics and supportive therapy are recommended for treatment. Gram staining may affect the treatment process, but ceftraixone, carbapenem, and aminoglycoside are preferred in the initial treatment of complicated cystitis(5). We know that EC can sometimes accompany pyelonephritis and may progress clinically to the point where a nephrectomy is required (11). The findings for our patient were compatible with EC, and the diagnosis was confirmed by performing a CT examination along with other routine examinations. In our patient, pyelonephritis was not considered by the urology and infectious diseases physicians. No pathology was detected in either kidney with CT, and the patient was discharged with hydration and antibiotic therapy. Although emphysematous cholecystitis is very rare, it should be considered in the differential diagnosis of diabetic patients who are admitted to the hospital and we suspect urinary tract infection, as there is a risk of developing complications.

Conclusion

When evaluating urinary system infections in diabetic patients, EC should be included in the differential diagnosis. With hospitalization and effective treatment, the disease can be treated before it progresses to sepsis.

References

1. Nokay M, Oğul L, Çıra DK et al. Emphysematous Cystitis: A Rare Cause of Abdominal Pain. Akd Med J. 2020; 6(2): 314-316.
2. Choi J, Choi S-K, Lee S-H et al. Clinical Outcomes and Risk Factor Analysis of Patients Presenting with Emphysematous Cystitis: A 15-Year Retrospective Multicenter Study. Medicina. 2021; 57(6):531. https://doi.org/10.3390/medicina57060531.
3. Schicho A, Stroszczynski C, Wiggermann P. Emphysematous cystitis: Mortality, risk factors, and pathogens of a rare disease. Clin. Pract. 2017;7:54-5.
4. Thomas AA, Lane BR, Thomas AZ et al. Emphysematous cystitis: a review of 135 cases. BJU Int. 2007;100: 17-20.
5. Amano M, Shimizu T. Emphysematous Cystitis: A Review of the Literature. 2014;53(2):79-82. https://doi.org/10.2169/internalmedicine.53.1121.
6. Okada S, Ichimura Y, Linuma M. Emphysematous cystitis due to Streptococcus salivarius infection in a patient with a neurogenic bladder. IDCases. 2022;27: e01410. https://doi.org/:10.1016/j.idcr.2022.e01410.
7. Grupper M, Kravtsov A, Potasman I. Emphysematous cystitis: Illustrative case report and review of the literature. Medicine (Baltimore) 2007; 86(1):47-53. https://doi.org/10.1097/MD.0b013e3180307c3a.
8. Noda R, Nishinarita J, Araki K et al. Emphysematous Cystitis Caused by Dysuria due to Sulpiride in a Patient with Chronic Kidney Disease: a Case Report. SN Compr. Clin. Med. 2022;4:97. https://doi.org/s42399-022- 01180-7.
9. Obeidat N, Al-Omari MH, Shwayyat B. Showering gas bubbles within the inferior vena cava detected sonographically can unmask a hidden infection: a case report of a rare presentation in a patient with emphysematous cystitis. J Ultrasound (2022). (Ahead of print). https//doi.org/10.1007/s40477-022-00673-4.
10. Tsakaldimis G, Bousiou Z, Dimou-Besikli S et al. Pneumomediastinum as a rare complication in an immunosuppressed patient with emphysematous cystitis. Clin Case Rep.

2022; 10(2):e05429. https://doi.org/10.1002/ccr3.5429.

11. Yıldız H. Coexistence of Rare Emphysematous Pyelonephritis and Cystitis in Uncontrolled Diabetes Mellitus Case: Case Report and Literature Review. KSÜ Med Fac. Journal. 2019;14(2): 85-88.

Experimental and Applied Medical Science, 3,3: 375-383, 2022. DOI 10.46871/eams.2022.43

Is The Level Of Knowledge Of Healthcare Workers About Hepatitis A, B, C Transmission Routes Sufficient?

Safiye Koculu Demir[1], Ozgur Onal[2], Hakan Kutlu[3], Adem Albayrak[4], Zuhal Yesilbag[5]

[1]*Demiroğlu Bilim University School Of Medicine, Department Of Infectious Diseases And Clinical Microbiology Istanbul, Turkey*
[2]*Süleyman Demirel University School Of Medicine, Department Of Public Health, Isparta, Turkey*
[3] *Acıbadem Hospital, Infectious Diseases And Clinical Microbiology, Ankara, Turkey*
Infectious Diseases And Clinical Microbiology, Turkey
[4]*Ankara University School Of Medicine, Department Of Infectious Diseases And Clinical Microbiology Ankara, Turkey*
[5]*Bakirkoy Dr. Sadi Konuk Training & Research Hospital İnfectious Diseases And Clinical Microbiology, Istanbul, Turkey*

Abstract

As with all infectious diseases, healthcare professionals should have sufficient knowledge to protect themselves, their colleagues and patients, and to inform patients and their relatives correctly about viral hepatitis. In this study, it was aimed to determine the level of knowledge about hepatitis A, B and C transmission routes of healthcare workers who are at high risk compared to the rest of the population. In this descriptive study, questionnaire was distributed to 600 people including employees and intern students. The data obtained from the questionnaire made by face-to-face interviews with 420 people who volunteered to participate in the research were evaluated in the study. In the survey study, the participants were asked a total of 66 questions, 22 in each area, to determine their level of knowledge about Hepatitis A, B and C. Participants were asked to mark one of the true/false/unknown option for the question specified in each item. Of the 420 people who participated in the survey, 345 (82.2%) were female and 75 (17.8%) were male, and the average age was found to be 30.05±10.51 years old. It was determined that the participants had an average of 5.44±5.65 years of work experience. As a result of the ANOVA and Post Hoc Tukey test, it was determined that the hepatitis A, hepatitis B and hepatitis C knowledge levels of the participants were statistically significantly different from each other. (mean±SD, respectively; 53.44±16.05, 68.22±20.6, 64.65±25.36) ($p<0.001$). In researches measuring the level of knowledge, deficiencies are determined and educational activities are shaped to eliminate these deficiencies. In our study, it was determined that the level of knowledge of HAV was especially lower in all participants compared to knowledge of HBV and HCV. For this reason, it is necessary to give priority to HBV and HCV in educational activities of HAV, which causes water and food-borne epidemics in cases such as earthquakes and disasters.

Keywords: *Hepatitis, patient's relatives, knowledge level, risk perceptions*

***Corresponding author:** Safiye Koçulu Demir. e-mail: safiyekoculu@gmail.com. ORCID ID: 0000-0003-4918-2258.

Introduction

Viral hepatitis are preventable contagious diseases that cause serious labor and economic losses, and that concern the whole society, not only the individual. Despite the developments in science and technology, it continues to be a health problem that maintains its importance all over the world. Hepatitis A virus (HAV) is transmitted from person to person by direct contact, contaminated food or water-borne faecal-oral route (1). Hepatitis B virus (HBV) and Hepatitis C virus (HCV) can be transmitted through blood, sexual intercourse, during birth from mother to baby, use of infected blood or blood products, inadequate sterilization of medical devices, sharing of items such as syringes, razors, toothbrushes, and during tattooing (2-5).

Viral hepatitis can start with acute hepatitis and cause chronic hepatitis, cirrhosis, liver failure, liver cancer and death. In our country, it is reported that HBV infection is responsible for 30- 40% of cirrhosis cases, 40-50% of liver cancer, and HCV infection is responsible for 25% of cirrhosis cases and 25-30% of liver cancer (6). Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide, with more than 780,000 deaths in2018. With a 5-year survival rate of 18%, HCC is the second deadliest tumor after pancreatic cancer (7).

The risk of contracting diseases transmitted in this way increases as healthcare workers have more sharp-object related and puncture wounds which increases contact with blood and body fluids (8,9). As with all infectious diseases, healthcare professionals should have sufficient knowledge to protect themselves, their colleagues and patients, and to inform patients and their relatives correctly about viral hepatitis. In this study, it was aimed to determine the level of knowledge about hepatitis A, B and C transmission routes of healthcare workers who are at high risk compared to the rest of the population.

Materials and Methods

In this descriptive study, questionnaire was distributed to 600 people at Giresun Prof. Dr. İlhan Özdemir State Hospital and Dr. Ali Menekşe Chest Diseases Hospital, including employees and intern students. The data obtained from the questionnaire made by face-to-face interviews with 420 people who volunteered to participate in the research were evaluated in the study. In the survey study, the participants were asked a total of 66 questions, 22 in each area, to determine their level of knowledge about Hepatitis A, B and C. Participants were asked to mark one of the true/false/unknown option for the question specified in each item. It was accepted that the participants who answered correctly to all the questions asked got 100 points each for Hepatitis A, B and C. Incorrect and "unknown" answers were given 0 points. (10).

Using the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) statistical program of the obtained data, numbers and percentages for discrete variables, mean + standard deviation values for continuous variables were given. Pearson's Chi-square, Mann Whitney U test, Kruskal Wallis tests were used for statistical analysis and $P<0.05$ was accepted for statistical significance.

Results

Of the 420 people who participated in the survey, 345 (82.2%) were female and 75 (17.8%) were male, and the average age was found to be 30.05±10.51 years old. It was determined that the participants had an average of 5.44±5.65 years of work experience. Table 1 shows the demographic characteristics of the participants in the study When the awareness of the participants about immunity against hepatitis A and hepatitis B virus was evaluated; 9.5% stated that they were naturally immune to hepatitis A, 29.8% stated that they had no immunity and did not get vaccinated, 20.2% were vaccinated, and 40.5% did not know. Against hepatitis B, 12.2% of the participants stated that they were naturally immune, 61.4% were vaccinated, and 26.4% did not know their current immune status.

81% of the participants answered correctly about hepatitis A transmission that drinking infected water, 80.7% by poorly washed vegetables, 68.3% by shared kitchen utensils, 56% by sexual intercourse, 52.9% by dental treatment, 36.4% by sharing the same social environment. It is true that 94.5% of the participants answered correctly about Hepatitis B transmission by infected by needle sticking, 90.0% by sexual intercourse, 83.6% by dental treatment, 83.6% by common nail clippers, 87.9% by razor blades. The correct answer rate for Hepatitis B can not be transmitted were 51.4% via contacted infected blood with intact skin, 86.2% via handshake, 50.2% via drinking infected water, 28.3% via mosquito bite, 48% via eating infected food. 87.4% knew correctly that the hepatitis B vaccine was available and 72.8% correctly knew that the disease could become chronic.

Table 1. Demographic characteristics of the participants

		n	%
Sex	Female	345	82,2
	Male	75	17,8
Occupation	MYO student	40	9,5
	midwifery student	121	28,8
	Laboratory worker	17	4,0
	Cleaning personnel	54	12,9
	Nurse	178	42,4
	Doctor	10	2,4
Education Level	Primary and secondary education	40	9,5
	High School	148	35,2
	University	232	55,3
Workplace	State Hospital	230	54,8
	Vocational Higher Education School	40	9,5
	Vocational High School	58	13,8
	Diğer	92	21,9
Marital Status	Married	217	51,7
	Single	203	48,3
Got Trained?	Yes	234	55,7
	No	186	44,3
Total		420	100,0

The ratio of participants which correctly knew that hepatitis C can be transmitted were 90% via needle sticks, 85% via sexual intercourse, 81.9% via dental treatment, 77.4% via common nail clippers, 72.1% via nail file, 83.6% via razor blade. The ratio of participants who correctly answered that hepatitis C can not be transmitted were 49.8% via the contact of infected blood with intact skin, 78.6% via handshake, 27.9% via mosquito bite, 51.9% via infected food. 51.1% knew correctly that there was no hepatitis C vaccine and 68.7% of them knew correctly that the disease could become chronic. The knowledge levels of the participants about the transmission and immunization of hepatitis A, B, C are given in Table 2.

Table 2. Knowledge levels about hepatitis transmission and immunization

	HAV Correct		**HBV** Correct		**HCV** Correct	
	n	%	n	%	n	%
1-Contact of intact skin with infected blood	128	30,5	248	51,4	209	49,8
2-The patient's needle sticking	253	60,2	397	94,5	378	90
3-Sexual intercourse	235	56,0	378	90	357	85
4-During dental treatment	222	52,9	351	83,6	344	81,9
5-Handshake	108	25,7	362	86,2	330	78,6
6-Kissing on the cheek	107	25,5	348	82,9	323	76,9
7-Mosquito bite	171	40,7	119	28,3	117	27,9
8-Drinking infected water	340	81,0	211	50,2	223	53,1
9-Eating unwashed vegetables and fruits	339	80,7	201	47,9	218	51,9
10-Using common nail clippers	254	60,5	351	83,6	325	77,4
11-Using common toothbrush	298	71,0	358	85,2	338	80,5
12-Using common rasp	218	51,9	331	78,8	303	72,1
13-Shaving razor	247	58,8	369	87,9	351	83,6
14-From mother to baby during birth	213	50,7	340	81	300	71,4
15-Inhalation	251	59,8	301	71,7	292	69,5
16-Use of common items, such as plates, with the sick person	287	68,3	198	47,1	188	44,8
17-Sharing the same social environment with the patient	153	36,4	282	67,1	283	67,4
18-Living in the same house increases the risk of transmission	326	77,6	270	64,3	252	60
19-May become chronic after acute infection	128	30,5	306	72,9	289	68,8
20-Vaccinated	349	83,1	367	87,4	215	51,2
21-Fecal transmission is extremely rare	136	32,4	234	55,7	198	47,1
22-It is transmitted through breast milk	175	41,7	186	44,3	141	33,6

The questions asked to determine the hepatitis A, B and C knowledge levels of the participants were evaluated out of 100, and the adequacy of the participants' knowledge level and the affecting factors are given in Table 3.

Tablo 3: Factors affecting the score of knowledge about hepatitis A, B and C viruses

		Hepatitis A Knowledge Score		**Hepatitis B Knowledge Score**		**Hepatitis C Knowledge Score**	
		med±SD	**p**	**med±SD**	**p**	**med±SD**	**p**
Sex	Male	55,65±18,10	0,192	63,01±19,83	**0,016**	59,09±23,80	**0,037**
	Female	52,97±15,56		69,34±0,67		65,84±25,55	
Occupation	MYO student	45,00±13,17	**<0,001**	72,71±14,83	**<0,001**	66,25±21,74	**<0,001**
	Midwife	55,06±14,17		72,66±20,98		72,73±22,63	
	Laboratory worker	67,11±13,01		76,47±8,06		79,41±9,25	
	Cleaning personnel	57,49±17,37		61,50±22,22		59,68±21,68	
	Doctor	45,00±9,69		85,42±6,87		84,55±8,35	
	midwifery student	50,83±17,58		60,64±19,70		50,75±27,28	
Education Level	Primary and Secondary School	57,37±18,32	0,101	58,45±24,62	**<0,001**	57,25±24,16	**<0,001**
	High School	51,56±16,72		62,08±18,94		53,81±26,38	
	University	54,02±15,11		73,68±19,38		72,73±21,79	
Workplace	State Hospital	56,50±14,83	**<0,001**	70,71±21,65	**0,002**	70,85±23,13	**<0,001**
	Vocational Higher Education School	45,00±13,17		72,71±14,83		66,25±21,74	
	Vocational High School	49,84±14,77		64,44±20,31		57,52±25,22	
	Other	51,73±18,84		62,45±19,02		52,96±27,29	
Marital status	Married	55,57±15,19	**0,005**	70,12±22,08	0,051	70,28±23,23	**<0,001**
	Single	51,16±16,65		66,19±18,83		58,64±26,19	
Got Trained?	No	53,02±15,78		63,76±22,38		57,32±28,33	
	Yes	53,67±15,46	0,692	71,14±19,57	**0,001**	69,13±22,91	**<0,001**
	TOTAL	53,44±16,05		68,22±20,64		64,65±25,36	

When the knowledge level of hepatitis A, B, C was evaluated with the post hoc Tukey test according to the affecting factors: According to the occupational groups; The factor that provides significance for hepatitis A knowledge status is that vocational higher education school students have lower scores than nurses, laboratory workers and cleaning personnel. The factor that provides significance for the hepatitis B knowledge status is that doctors and nurses score higher than midwifery students and cleaning staff. In addition, laboratory workers score higher than midwifery students. The factor that provides significance for the hepatitis C knowledge status is that doctors, nurses, and laboratory workers score higher than midwifery students and cleaning staff.

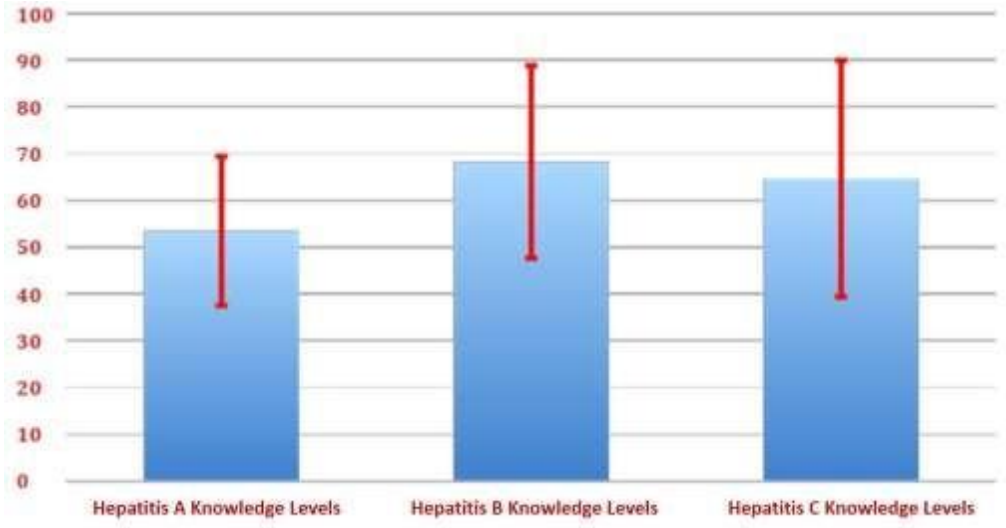
According to educational status; The factor that provides significance for the hepatitis B and hepatitis C knowledge status is that university graduates score higher than high school, secondary and primary school graduates. According to the results of the institution being worked for; The factor that provides significance for the hepatitis A knowledge status is that those working in the State Hospital have higher scores than those working in the Vocational Higher Education School and Vocational High School. The factor that provides significance for the hepatitis B knowledge status is that the employees of the State Hospital have higher scores than the other group. The factor that provides significance for the hepatitis C knowledge status is that State Hospital employees have higher scores than the vocational high school and other groups. A moderately positive and significant correlation was found between hepatitis A, B, C knowledge level and age (table 4)

Table 4. Correlation between hepatitis A, B, C knowledge level and age

	Hepatitis A **r-p**	**Hepatitis B** **r-p**	**Hepatitis C** **r-p**
Age	**0,232-<0,001**	**0,106-0,030**	**0,265-<0,001**
Hepatitis A	**1**	**0,198-<0,001**	**0,177-<0,001**
Hepatitis B		**1**	**0,817-<0,001**
Hepatitis C			**1**

As a result of the ANOVA and Post Hoc Tukey test, it was determined that the hepatitis A, hepatitis B and hepatitis C knowledge levels of the participants were statistically significantly different from each other. (mean±SD, respectively; 53.44±16.05, 68.22±20.6, 64.65±25.36) ($p<0.001$) (Figure 1)

Figure 1 Comparison of hepatitis A, B, C knowledge levels



Discussion

Viral hepatitis is the leading cause of liver cancer and liver transplants. The first step for the prevention and protection of viral hepatitis is to have sufficient awareness and knowledge about the disease (6).

Turkey is located in the middle endemic region for hepatitis A. Infection often peaks in late childhood and adolescence. Outbreaks caused by infected water and food are common (11,12,13). In the study conducted by Aslı et al. (14), the rate of hepatitis A seroprevalence was found to be 50% between the ages of 0-30, and 89% in those over the age of 46. The low rate of seropositivity in the younger age group makes this group more risky for HAV infection. Although the childhood immunization strategy with hepatitis A vaccine seems to be effective in reducing the reported incidence of hepatitis A in individuals younger than 19 years of age, it has been observed that people over 20 years of age are the most susceptible population (15). In our study, the mean age of the participants was 30.05±10.51, and they are in the risky group. 9.5% of the respondents in the survey answered that they are naturally immune to hepatitis A, 29.8% have never been immune and have not been vaccinated, 20.2% are vaccinated, and 40.5% do not know their status. Hepatitis A preventive and control measures need to focus on adults, in addition to the current childhood hepatitis A vaccination program.

Göktalay et al. (16); in the study he carried out to measure the knowledge levels of hepatitis B knowledge among 392 faculty and college students, he determined that 71.4% knew correctly about blood route transmission, 57.0% knew correctly the sexual transmission, and 56% knew correctly about from mother to baby transmission during birth. 37.4% of the participants answered correctly that it could not be transmitted via water and food. According to Ersoy et al. (17), in another study in which 195 midwives participated, 99.5% answered correctly that hepatitis B can be transmitted by blood, 93.8% answered correctly that it can be transmitted from mother to baby during birth, and 97.4% answered correctly that it can be transmitted during tooth extraction. Only 27.8% of the participants correctly knew that hepatitis B would not be transmitted by using common plates and 39% knew that it can not be transmitted by kissing. In our study; the correct answer rate for knowing that it can be transmitted via needle stick was 94.5%, via sexual intercourse is 90.0%, via dental treatment was 83.6%, via common nail clippers usage was 83.6%, via razor blades was 87.9%. The correct answer rate for no infection transmission via the following ways were: infected blood with intact skin (51.4%), handshake (86.2%), drinking infected water (50.2%), mosquito bite (28.3%), eating infected food(48%).

In a study measuring the level of knowledge of the personnel providing primary health care services, it was reported that the transmission routes of hepatitis B infection were answered correctly by 73% (18). Ersoy et al. (17) found the rate of those who knew all the transmission routes correctly to be 45%, and this rate was quite low and it was interpreted that the study only included midwives, which may have caused the level of knowledge to appear low. In our study, it was conducted for all healthcare professionals and 50% correct answers for all the questions were evaluated as adequate knowledge level. When the adequacy of knowledge levels were evaluated, it was remarkable that HAV knowledge levels were lower than HBV and HCV ($p<0.001$). Compared to other studies, the level of HBV knowledge was not found to be high.

The CDC estimates that approximately 385,000 sharp objects related injuries occur annually among healthcare workers in hospitals (19). According to the data obtained from the Exposure Prevention Network (EPINet), when the rates reported in 2018 and the rates in 2014 are compared, the risk of sharp objects injuries increased by 20% (20), and the risk of contact with infected blood and body fluids increased by 42% (21).

In our study, when hepatitis A, B, C knowledge levels were compared in terms of gender, no statistically significant difference was found between men and women.

In a study measuring the hepatitis B knowledge levels of students in faculty of health personnel and higher education students, the average correct answers was found to be higher in those whostated that they had knowledge about the disease compared to those who did not (16).

Similarly, in our study, the level of knowledge was found to be higher in those who received previous education about Hepatitis B and C ($p<0.01$). No statistically significant difference was found between those who received and who did not receive education in hepatitis A ($p< 0.692$). In a study investigating the knowledge levels of general practitioners about hepatitis B and hepatitis C (22); it has been determined that the level of knowledge about HCV infections is lower than the level of knowledge about HBV infections. Similar results were found in our study.

When the health workers and students were compared, no difference was found between the hepatitis A knowledge levels, while the hepatitis B and hepatitis C knowledge levels werefound to be significantly higher in the health care workers ($p=0.35$, $p=0.05$, $p<0.01$). This situation has been associated with the provision of compulsory in-service training for sharp objects wounds and infectious diseases to the hospital staff and hence, the increase in awareness. In our study, a moderately positive and significant relationship was found between hepatitis A, B, C knowledge level and age. Since the average age of health workers is higher than that of students, this supports the fact that the knowledge level increased with age. The lowest correct answer was given to the question that it won't be transmitted via infected blood contact with intact skin and mosquito bite.

Conclusion

In researches measuring the level of knowledge, deficiencies are determined and educational activities are shaped to eliminate these deficiencies. In our study, it was determined that the level of knowledge of HAV was especially lower in all participants compared to knowledge of HBV and HCV. For this reason, it is necessary to give priority to HBV and HCV in educationalactivities of HAV, which causes water and food-borne epidemics in cases such as earthquakes and disaster.

References

1. Barrett CE, Pape BJ, Benedict KM, et al. Impact of Public Health Interventions on Drinking Water- Associated Outbreaks of Hepatitis A - United States, 1971-2017. MMWR Morb Mortal Wkly Rep 2019; 68:766.
2. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B andC virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015;21:1020-1026.
3. Dursun M, Ozekinci T, Ertem M, et al. Prevalence of hepatitis C in adults in the south-eastern region ofAnatolia: a community-based study. Hepatol Res. 2004; 29(2): 75-80.
4. Yildirim B, Barut S, Bulut Y, et al. Seroprevalence of hepatitis B and C viruses in the province of Tokat inthe Black Sea region of Turkey: A population-based study. Turk J Gastroenterol. 2009; 20(1): 27-30.
5. Erbay K, Hızel K, Özdilet T. Anti-HCV Screening Before Surgery. Klimik J. 2019; 32(3): 229-32.
6. Republic of Turkey Ministry of Health General Directorate of Public Health. Turkey Viral Hepatitis Prevention and Control Program 2018–2023. Ankara: T.C. Ministry of Health, General Directorate of Public Health, Department of Communicable Diseases and Vaccine Preventable Diseases Department; 2018. [Access Date: 09.12.2020] https://hsgm.saglik.gov.tr/depo/birimler/Bulasici-hastaliklar-db/duyurular/Turkiye_Viral_Hepatit_Onleme_ve_Kontrol_Programi/Turkiye_Viral_Hepatit_Onleme_ve_Ko ntrol_Programi_TR.pdf
7. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014,Featuring Survival. J Natl Cancer Inst 2017; 109.
8. Akkaya S, Şengöz G, Pehlivanoğlu F, Güngör-Özdemir E, Akkaya Tek Ş. Evaluation of the survey resultsrelated to sharp and stab wounds. Klimik J. 2014; 27(3): 95-8.
9. Bozkurt S, Kökoğlu ÖF, Yanıt F, et al. Injuries with needle sticks and surgical instruments in healthcareworkers. Dicle Med J. 2013; 40(3): 449-52.
10. Bilge N, Demir P. Evaluation of Food Safety Knowledge Among Food Handlers. Van Vet J. 2019; 30 (1): 7-12.
11. Çopur Çiçek A, Özkasap S, Dereci S ,Şahin K, Dilek A.R, Gündoğdu Ulusan D.Z, Ertürk A. Hepatitis A, Band C Seroprevalence in Pediatric Patients in Rize Province. Viral Hepat J. 2012; 18(3): 102-6.
12. Ertürk A, Çopur Çiçek A, Cüre E, Akdoğan RA, Öztürk Ç. Hepatitis A seroprevalence in adult age groups inRize Province. Viral Hepat J. 2013; 19(2): 85-8.
13. Yamazhan T. Hepatitis A: Epidemiology, Transmission and Prevention Turkiye Klinikleri JGastroenterohepatol-Special Topics 2010;3(1)
14. Karadeniz A. , Akduman Alaşehir E. , Yeşilbağ Z. , Balıkçı A. , Yaman G. The seroprevalence of hepatitis Ain Istanbul, Turkey. Marmara Med J. 2017; 30(1): 14-17.
15. Wang Z, Chen Y, Xie S, Lv H. Changing Epidemiological Characteristics of Hepatitis A in ZhejiangProvince, China: Increased Susceptibility in Adults. PLoS One 2016; 11:e0153804.
16. Göktalay T, Özyurt Cengiz B. Hepatitis B Seroprevalence and Hepatitis B knowledge levels in faculty and college students training health personnel at Celal Bayar University.Viral Hepat J. 2010; 15(1): 13-21
17. Ersoy Y, Ilgar M, Güneş G. Knowledge level of midwives in terms of Hepatitis B in Malatya region. İnönü University Med J. 2005;12(3):159-62.
18. Maral I, Özkan S, Aybay C, Bumini MA. Viral hepatitis A, B, C and E seroprevalence in healthcare personnel working in primary care and the personnel's knowledge of the transmission routes of these infections. Journal of İnfection 1999; 13(1): 89-93.

19. Centers for Disease Control and Prevention. Sharps Safety for Healthcare Settings. https://www.cdc.gov/sharpssafety/ (Accessed on November 19, 2021).

20. International Safety Center. EPINet Report for Needlestick and Sharp Object Injuries, 2018.https://internationalsafetycenter.org/wp-content/uploads/2019/07/Official-2018-US-NeedleSummary- FINAL.pdf.),

21. International Safety Center. EPINet Report for Needlestick and Sharp Object Injuries, 2018.https://internationalsafetycenter.org/wp-content/uploads/2019/07/Official-2018-US-NeedleSummary- FINAL.pdf.),

22. Knowledge levels of general practitioners about hepatitis B and hepatitis C. Academic Journal of Gastroenterology. 2012; 11(2): 58-62.

Experimental and Applied Medical Science, 3,3: 384-394, 2022. DOI 10.46871/eams.2022.44

The Effect of Nursing and Midwifery Students Attitudes Toward Information and Communication Technologies on Their Readiness for Mobile Learning

Aliye Bulut[1], Sema İcel[2], Zehra Cercer

[1]Gaziantep Islam Science and Technology University, Faculty of Medicine, Dept. of Public Health, Gaziantep/ Turkey

[2]Gaziantep Islam Science and Technology University, Faculty of Health Sciences, Dept. of Midwifery, Gaziantep/ Turkey

Abstract

The present study was conducted to determine how nursing and midwifery students' attitudes toward information and communication technologies affected their readiness for mobile learning. The population consisted of all the students studying in the Departments of Midwifery and Nursing, Faculty of Health Sciences, Gaziantep Islam Science and Technology University. A personal information form, which was prepared by the researchers upon the literature review and includes questions about the socio-demographic data of the students as well as the Information and Communication Technology Attitude Scale and the Mobile Learning Readiness Scale were used to collect the data (N=292). 62.5% of the participants were aged between 17-19 years. 83.7% of the participants were female and the remainder were male (n=283). The results of this study revealed that the students were partially/moderately ready for mobile learning. The students obtained a medium-high score concerning attitudes toward information and communication technologies. Consequently, based on findings of the present study and other studies, we think that online learning, e-learning and mobile learning environments have become more common in today's higher education system and it is necessary to assess experience, perception, attitude, skill, and readiness for these environments and to improve them along with the advancements in information and communication technologies.

Key words: *Mobile Learning, Information and Communication Technologies, Midwifery, Nursing, Attitude.*

** This paper was produced from project (number: 2021-TS-03) supported by The Scientific Research Projects Coordination Unit of Gaziantep Islamic Science and Technology University.*

***Corresponding author:** Aliye Bulut. e-mail: aliyedemirok@yahoo.com. ORCID ID:0000-0002-4326-0000.

1. Introduction

Computers and mobile technologies are time-saving, portable, and useful in many ways, thus resulting in becoming an essential part of people's lives (1,2). In a digitalizing world, people can quickly satisfy their learning and information needs by using computer and mobile technologies (3-5).

Mobile technologies have started to take their place in education systems because information can be easily accessed anytime and anywhere. Hence, students can maintain their learning activities through mobile learning even when face-to-face teaching is not possible (6). Mobile (or M-) learning refers to a form of learning that provides access to information through mobile technology without being tied to any specific location and is designed around the education that individuals need (7).

Technological advancements will be definitely more visible in the field of health in days to come, as are today (7). The use of mobile technology and learning has become more common in nursing and midwifery education, as in other areas (7, 8). Following developments in information and communication technologies (ICTs) and adapting mobile learning to nursing/midwifery education are predicted to be beneficial for an effective and rapid learning (3, 4, 9).

The recent increase in digitalization of education has led students and instructors to use mobile learning environments (10).

Meanwhile, as long as students have exhibited positive attitudes toward information and communication technologies and have become ready for mobile learning, they benefit from the effectiveness of learning environments more (3, 4, 9). This situation has required nurses and midwife instructors to conduct studies on information and communication technologies and mobile learning (7, 8).

Although students' attitudes toward information and communication technologies and their readiness for mobile learning have been studied, there is a limited number of studies on this subject. In the literature, no study has been found that included both nursing and midwifery students and investigated the effect of their attitudes toward information and communication technologies on their readiness for mobile learning. Once this objective is achieved, their competence in information technology and mobile learning and their attitudes towards them as well as the relationship of their competence and attitudes with socio-demographic factors can be determined and the related education plans can be made. In this context, the present study was conducted to determine how nursing and midwifery students' attitudes toward information and communication technologies affected their readiness for mobile learning.

2. Material and Methods

2.1. Location: Gaziantep Islam Science and Technology University, Faculty of Health Sciences

2.2. Time: The study was conducted between June 2021 and June 2022.

2.3. Population and sample: The population consisted of all the students studying in the Department of Midwifery and Nursing, Faculty of Health Sciences, Gaziantep Islam Science and Technology University (N=292). The sample consisted of the students who agreed to participate in the study (n=283).

Inclusion criteria were determined as follows;

- Being a student studying at Midwifery or Nursing Department of Gaziantep Islam Science and Technology University, Faculty of Health Sciences.
- Agreeing to participate in the study.

Exclusion criterion was below;

- Students who requested to withdraw from the study during the data collection process were not included in the study.

2.4. Design: This is a descriptive and cross-sectional study.

2.5. Those contributing to the study: The researchers took part in every stage of the study.

2.6. Data collection tools: A personal information form, which was prepared by the researchers upon the literature review and includes questions about the socio-demographic characteristics of the students as well as the Information and Communication Technology Attitude Scale and the Mobile Learning Readiness Scale were used to collect the data (1, 10). **Personal Information Form**; The form includes a total of 11 questions about the students' age, gender, family type, university year, and status of using internet, mobile device, and technology.

Information and Communication Technology Attitude Scale (ICTAS); The scale was developed by Günbatar. This five-point Likert type scale has 23 items and five subscales ("general tendency of ICT ", "access to information in virtual environment", "computer hardware", "use of software", and "communication in virtual environment") (10).

Mobile Learning Readiness Scale (MLRS)*;* Lin et al., (2016) developed the scale to determine the readiness of nursing students for mobile learning and Gökçearslan et al., (2017) adapted it to Turkish and conducted its validity and reliability study. While the original version of the scale has 19 items, its Turkish version has 17 items. The scale items are grouped under three subscales; "self-sufficiency (items 1-2-3-4-5-6), optimism (items 7-8-9- 10-11-12-13), and self-learning (items 14-15-16-17)". The Cronbach's alpha coefficient of the scale is 0.95. The items are rated in 7-point Likert type scale, ranging between (1) "strongly disagree" and (7) "strongly agree". The lowest and highest scores of the scale are 17 and 119 points, respectively (1).

2.7. Data Collection: The participants gave their consent by marking the statement "I agree to participate in the study" on the form. The data were collected by sending the data collection tools to the students through Google forms.

2.8 Data analysis: Statistical analysis of the data was performed using SPSS 22 software. The data were assessed at the confidence interval of 95% and significance level of 0.05. The distribution of the scale scores to the normal distribution was examined by Kolmogrov
Smirnov and Shapiro Wilks test, and their distribution was found to be suitable for normal distribution.

3.Findings

The results of the study indicated that 62.5% of the participants were aged between 17-19 years. 83.7% of them were female and the remainder were male. Table 1 shows socio-demographic characteristics of the participants.

Table 1. Some socio-demographic characteristics of the participants (N=283)

Socio-demographic Characteristics		**Number**	**%**
Age	17-19 years	177	62.5
	20-25 years	106	37.5
Gender	Female	237	83.7
	Male	46	16.3
Family Type	Nuclear Family	214	75.6
	Extended Family	69	24.4
Department	Midwifery	96	33.9
	Nursing	187	66.1
University year	1	142	50.2
	2	141	49.8

Table 2 shows the participants' status of using the internet, mobile device, and information and communication technology. 20.8% of the participants were connecting the internet or using mobile devices or information and communication technology for 6 or more hours. When the participants' reasons for using mobile devices were examined, 48.1% of them stated that they were using their mobile devices for communication purposes.

Table 3 shows the data on the readiness of the participants for mobile learning. There was a significant difference between their MLRS total scores in terms of the reason for using mobile devices and what devices they most used during their courses ($p<0.05$). The results of the TUKEY test applied to determine which group caused the difference indicated that the readiness level was significantly higher in those who were able to use mobile devices moderately than those who had poor ability to use mobile devices. Also, those who had good and very good ability to use these devices had a significantly higher level of readiness when compared to their counterparts with poor and very poor ability.

The readiness level of those who used most frequently smartphones, laptops, and tablets during their distance education courses was significantly higher than that of those who used desktop computers most frequently. Table 3 shows the data on the readiness of the participants for mobile learning.

There was a significant difference between their MLRS total scores in terms of the reason for using mobile devices and what devices they most used during their courses ($p<0.05$). The results of the TUKEY test applied to determine which group caused the difference indicated that the readiness level was significantly higher in those who were able to use mobile devices moderately than those who had poor ability to use mobile devices. Also, those who had good and very good ability to use these devices had a significantly higher level of readiness when compared to their counterparts with poor and very poor ability.

Table 2. The Participants' status of using Internet, Mobile Device, and Information and Communication Technology (N=283)

Characteristics		**Number**	**%**
How much time did you spend in front of a screen every day?	1 hour	11	3.9
	2 hours	36	12.7
	3 hours	55	19.4
	4 hours	63	22.3
	5 hours	59	20.8
	6 and longer	59	20.8
Ability to use mobile devices	Very poor	1	0.4
	Poor	10	3.5
	Moderate	154	54.4
	Good	96	33.9
	Very good	22	7.8
Reason for using mobile devices	Shopping	2	0.7
	Training and research	99	35.0
	Amusement	46	16.3
	Communication	136	48.1
What device did you use most during your distance undergraduate courses?	Smartphone	249	88.0
	Laptop computer	20	7.1
	Desktop computer	3	1.1
	Tablet computer	11	3.9
How good is the internet access where you live?	It's very difficult to access the internet	31	11.0
	I can't always access the internet	87	30.7
	I can often access the internet	110	38.9
	I can always access the internet	55	19.4
How fast is the internet connection where you live?	Very slow	15	5.3
	Slow	115	40.6
	Fast	147	51.9
	Very fast	6	2.1

The readiness level of those who used most frequently smartphones, laptops, and tablets during their distance education courses was significantly higher than that of those who used desktop computers most frequently.

Table 3. Distribution of data on the participants' MLRS mean scores in terms of their socio-demographic characteristics (N=283)

Characteristics		Total Readiness		p
		Mean	Standard Deviation	
Age	17-19	66.25	25.60	0.319a
	20-25	69.43	26.55	
Gender	Female	67.05	25.64	0.562a
	Male	69.48	27.74	
Family type	Nuclear Family	68.89	26.59	0.099a
	Extended Family	62.96	23.50	
Department	Midwifery	65.84	25.69	0.459a
	Nursing	68.26	26.13	
Grade	1	67.60	25.40	0.919a
	2	67.28	26.60	
How much time were you spending per day in front of a screen?	1 hour	67.45	25.66	0.378b
	2 hours	63.33	26.69	
	3 hours	64.29	25.55	
	4 hours	72.67	24.32	
	5 hours	64.90	27.07	
	6 hours and longer	69.85	26.42	
Ability to use mobile devices	Very poor			0.000b*
	Poor	46.50	17.71	
	Moderate	62.69	22.88	
	Good	74.25	26.76	
	Very good	81.00	32.84	
Reason for using mobile devices	Shopping	105.00	8.49	0.109b
	Training and research	67.81	28.91	
	Amusement	62.48	25.38	
	Communication	68.30	23.58	
What device did you most use in your undergraduate classes during distance education?	Smartphone	66.98	25.96	0.013b*
	Laptop computer	73.25	24.24	
	Desktop computer	26.33	15.31	
	Tablet computer	78.64	20.23	
How good is the internet access where you live?	It's very difficult to access the internet	58.13	26.50	0.101b
	I can't always access the internet	66.85	25.65	
	I can often access the internet	67.98	24.98	
	I can always access the internet	72.55	27.27	
How fast is the internet connection where you live?	Very slow	64.33	22.16	0.517b
	Slow	65.12	25.00	
	Fast	69.30	26.41	
	Very fast	74.17	41.39	

Table 4 shows the data related to the ICTAS scores of the participants. There was a significant difference between their ICTAS scores in terms of the time they spent in front of a screen every day, the ability to use mobile devices, and the status of accessing the internet where they lived ($p<0.05$). The results of the TUKEY test applied to determine which group caused the difference indicated that those who were spending 3, 4, and 6 or more hours in front of the screen every day had a significantly higher ICTAS total score compared to those who were spending 2 hours.

The ICTAS mean score was significantly higher in those who were able to use mobile devices at moderate, good, and very good levels than those who had poor ability to do. Moreover, those with good level of ability had a significantly higher ICTAS mean score compared to their counterparts with moderate level of ability. The ICTAS mean score was significantly higher in those who can't always access the internet when compared to those who had a hard time accessing the Internet. Furthermore, those who can always access the internet had a significantly higher ICTAS mean score than those who had a hard time accessing the Internet and those who can often access.

Table 4. Distribution of data on the participants' ICTAS mean scores in terms of their socio-demographic characteristics (N=283)

Characteristics		**Information Communication Technologies**		**p**
		Mean	**Standard Deviation**	
Age	17-19	71.09	19.42	0.191a
	20-25	74.22	19.42	
Gender	Female	72.33	18.82	0.895a
	Male	71.91	22.60	
Family type	Nuclear Family	73.43	19.21	0.076a
	Extended Family	68.65	19.87	
Department	Midwifery	72.31	19.99	0.975a
	Nursing	72.24	19.21	
Grade	1	71.15	19.06	0.334b
	2	73.38	19.83	
How much time were you spending per day in front of a screen?	1 hour	76.00	17.62	0.040b*
	2 hours	63.69	20.16	
	3 hours	72.71	19.52	
	4 hours	77.11	16.58	
	5 hours	71.17	19.73	
	6 hour and longer	72.29	20.64	
Ability to use mobile devices	Poor	47.90	13.56	0.000b*
	Moderate	69.66	19.17	
	Good	78.28	16.87	
	Very good	75.59	22.87	

Reason for using mobile devices	Shopping	95.00	8.49	0.159b
	Training and research	74.33	19.99	
	Amusement	69.30	20.94	
	Communication	71.42	18.39	
What device did you most use in your undergraduate classes during distance education?	Smartphone	71.51	19.45	0.118b
	Laptop computer	80.70	15.29	
	Desktop computer	60.67	34.27	
	Tablet computer	77.00	19.35	
How good is the internet access where you live?	It's very difficult to access the internet	65.13	19.98	0.011b*
	I can't always access the internet	73.43	19.30	
	I can often access the internet	70.29	19.21	
	I can always access the internet	78.38	18.36	
How fast is the internet connection where you live?	Very slow	71.00	21.79	0.661b
	Slow	70.82	18.68	
	Fast	73.29	19.62	
	Very fast	77.83	26.09	

Correlation analysis was performed to determine the correlation between the MLRS and the ICTAS, and the Pearson's correlation coefficient was obtained (Table 5). The overall MLRS had a positive significant correlation with the general tendency of ICT subscale by 57.4%, the access to information in virtual environment subscale by 60.1%, the computer hardware subscale by 13.5%, the use of software subscale by 49%, and the communication in virtual environment subscale by 41.6%.

Self-sufficiency subscale of MLRS had a positive significant correlation with the general tendency of ICT subscale by 55%, the access to information in virtual environment subscale by 54.1%, the computer hardware subscale by 14.8%, the use of software subscale by 48.4%, and the communication in virtual environment subscale by 38.7%.

Its optimism subscale had a positive significant correlation with the general tendency of ICT subscale by 54.7%, the access to information in virtual environment subscale by 58.8%, the use of software subscale by 45.7%, and the communication in virtual environment subscale by 38.1%.

Its self-learning subscale had a positive significant correlation with the general tendency of ICT subscale by 47.9%, the access to information in virtual environment subscale by 52.4%, the use of software subscale by 40.6%, and the communication in virtual environment subscale by 38.9%.

Table 5. Correlation between MLRS and ICTAS scores of the participants (N=283)

		General tendency of ICT	Access to information in virtual environment	Computer hardware	Use of software	Communication in virtual environment
Overall MLRS	r	.574**	.601**	.135*	.490**	.416**
	p	.000	.000	.023	.000	.000
Self-sufficiency	r	.550**	.541**	.148*	.484**	.387**
	p	.000	.000	.012	.000	.000
Optimism	r	.547**	.588**	.113	.457**	.381**
	p	.000	.000	.059	.000	.000
Self-learning	r	.479**	.524**	.111	.406**	.389**
	p	.000	.000	.063	.000	.000

4.Discussion

The results of this study were discussed with the relevant literature. In the present study, it was determined that most of the students were female. The similar studies reported that most of students were female (2,3,11,12). It can be asserted that this was associated with the fact that midwifery and nursing departments in Turkey are mostly preferred by female individuals. In this study, it was found that the students were partially/moderately ready for mobile learning. Among similar studies, the students were partially ready for mobile learning in the study by Yalçınkaya, most of the students were ready in the study by Zayim and Deniz, and the students were moderately ready in the study by Sırakaya and Alsancak Sırakaya (2,11,13). Different findings reported by in similar studies may have been associated with the course of technological advancements over time.

The results of the present study revealed that the students obtained a medium-high score from the ICTAS. In their study, Gündoğdu et al., stated that nursing students exhibited positive attitudes toward ICTs. In the study by Şahin et al., students' attitudes toward ICTs were highly positive. In another study conducted with nursing and midwifery students, they obtained low- medium scores from the ICTAS (2,4,14). In the light of these findings, it can be asserted that this result is associated with the fact that in this era, information and communication technologies are developing rapidly and university students show an intense interest in technological developments.

In the present study, no significant difference was found between the students' MLRS total and subscale scores and the variable of university year. Similar studies reported that there was a correlation between the university year and the scale scores (2,11,15).

Since the related university has recently been established, only first and second-year students have been studying. This is thought to be the cause of the difference.

In this study, it was determined that there was a significant difference between the students' MLRS total score and the most frequently used device by them. In the study by Yalçınkaya, it was reported that while there was no significant difference between using smartphone and the readiness scale total score, there was a significant difference between using laptop, desktop, and tablet computers and the readiness scale total score (11). The result might have been caused by the limited battery life and small screen size of smartphones.

In the present study, it was determined that there was a significant difference between the students' MLRS total score and their ability to use the mobile device. The readiness level of the students who were able to use mobile devices at very good and good levels was higher. It is suggested to organize trainings aiming to improve students' abilities to use mobile devices and information and communication technologies so that their readiness level can be elevated. In this study, it was determined that the total score of the scale was significantly higher in those who spent more times in front of the screen and were able to use mobile devices at very good and good levels. Likewise, in their study, Şahin et al., reported that when the students used the computer for longer period of times, their scale mean scores increased (4). It is an expected result that an individual who spends a great deal of time with technological devices has a positive tendency toward ICTs.

It was determined that the participants' levels in general tendency of ICT subscale of the ICTAS differed significantly in terms of the most frequently used device during distance education. The level of general tendency of ICT was significantly higher in those who used most frequently smartphones, laptop computers and tablet computers during distance education than their counterparts who used desktop computers most frequently. It was thought that general tendency of ICT increased since smartphones, tablets and laptops are portable and provide the opportunity to participate in educational environments at anytime.

In this study, it was found that the overall MLRS had a positive significant correlation with the general tendency of ICT subscale by 57.4%, the access to information in virtual environment subscale by 60.1%, the computer hardware subscale by 13.5%, the use of software subscale by 49%, and the communication in virtual environment subscale by 41.6%. Although there are studies examining the ICT-related skills, attitudes, and experiences of nursing and midwifery students, no study has been found that examines the correlation of ICT with mobile learning readiness. Therefore, the correlational analysis between the scales was discussed with the studies on different groups using similar scales.

A study examining education faculty students' attitudes toward distance education and readiness for e-learning in students from education faculty reported that there was a moderate correlation between attitude toward distance education and readiness for e-learning (16).

Likewise, the correlational analysis of the total and subscale scores of the scale revealed a moderate correlation. In Haznedar's study on university students, it was found that while the first-level variable predicting the skills of information and communication technologies was the experience of using computer, the first-level variable predicting the attitude toward e- learning was learning (17).

Consequently, based on findings of the present study and other studies, we think that online learning, e-learning and mobile learning environments have become more common in today's higher education system and it is necessary to assess experience, perception, attitude, skill, and readiness for these environments and to improve them along with the advancements in information and communication technologies.

References

1. Gökçearslan Ş, Solmaz E, Kukul V. Mobil Öğrenmeye Yönelik Hazırbulunuşluk Ölçeği: Bir Uyarlama Çalışması. Eğitim Teknolojisi Kuram ve Uygulama. 2017;7(1):143-157.
2. Zayım N, Özel D. Factors Affecting Nursing Students' Readiness and Perceptions Toward the Use of Mobile Technologies for Learning. Computers, Informatics, Nursing. 2015;33(10):456-464.
3. Çapık A, Çapık C, Kırbaş Y. Ebelik Ve Hemşirelik Bölümü Son Sınıf Öğrencilerinin Bilgi ve İletişim Teknolojilerine Yönelik Tutumlarının İncelenmesi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi. 2018;21(3):163-170.
4. Şahin E, Yavan T, Demirhan M, Aydın M, Yeşilçınar İ. Hemşirelik Öğrencilerinin Bilgi ve İletişim Teknolojilerine Yönelik Tutumlarının Belirlenmesi. KSBD. 2020;12(22):193-202.
5. Tütüncü D, İleri YY. Sağlık Bilimleri Fakültesi Öğrencilerinin Bilgi ve İletişim Teknolojilerine Bakışı Üzerine Bir Araştırma: Konya İli Örneği. Online Türk Sağlık Bilimleri Dergisi. 2021;6(1):92-101.
6. Kılınç H. Mobil öğrenme: eğitim ve öğrenimin dönüşümü. Açıköğretim Uygulamaları ve Araştırmaları Dergisi. 2015;1(4):132-138.
7. Şahin G, Başak T. Hemşirelikte mobil öğrenme "m-öğrenme". İnternational Journal of Human Sciences. 2017;14(4):4481-4491.
8. Aytur Özen T, Kantek F. Türkiye'de Hemşirelik Ve Teknoloji Alanında Yapılan Çalışmaların İncelenmesi. Uluslararası Sağlık Yönetimi Ve Stratejileri Araştırma Dergisi. 2020; 6(3):395-410.
9. Kim JH, Park H. Effects of Smartphone-Based Mobile Learning in Nursing Education: A Systematic Review and Meta-analysis. Korean Soc Nurs Sci. 2019;13(1):20-29. doi: 10.1016/j.anr.2019.01.005. Epub 2019 Jan 16. PMID: 30659927.
10. Günbatar MS. Bilgi ve iletişim teknolojilerine yönelik bir tutum ölçeği geliştirme çalışması. Ahi Evran Üniversitesi Kırşehir Eğitim Fakültesi Dergisi. 2014;15(1):121-135.
11. Yalçınkaya T. Hemşirelik Öğrencilerinin Mobil Öğrenmeye Yönelik Tutum Ve Hazırbulunuşluk Durumlarının İncelenmesi. Ege Üniversitesi Sağlık Bilimleri Enstitüsü. Yüksek Lisans tezi, 2019.
12. Yiğit Ü. Hemşirelik Öğrencilerinin Mobil Öğrenmeye Yönelik Tutumlarının Belirlenmesi. Abant Journal of Health Sciences and Technologies. 2021;1(1):24-33.
13. Sırakaya M, Alsancak Sırakaya D. Mobil öğrenmeye hazırbulunuşluğun akıllı telefon kullanımına göre incelenmesi. Mehmet Akif Ersoy Üniversitesi Eğitim Fakültesi Dergisi. 2021;57:362-381.
14. Gündoğdu H, Erol F, Tanrıkulu F, Yağmur Filiz N, Kuzgun H, Dikmen Y. Hemşirelik öğrencilerinin bilgi ve iletişim teknolojilerine yönelik tutumlarının incelenmesi. International

Journal of Human Sciences. 2018;15(1):441-450.
15. Özkütük N, Orgun F, Baysan A. The readiness of nursing students for mobile learning: a cross-sectional study. Contemp Nurse. 2021;57(3-4):202-212. doi: 10.1080/10376178.2021.1987940.
16. Yakar L, Yıldırım Yakar Z. Eğitim Fakültesi Öğrencilerinin Uzaktan Eğitime Karşı Tutumlarının ve E- Öğrenmeye Hazır Bulunuşluklarının İncelenmesi. Mersin Üniversitesi Eğitim Fakültesi Dergisi. 2021;17(1):1-21.
17. Haznedar Ö. Üniversite Öğrencilerinin Bilgi Ve İletişim Teknolojileri Becerilerinin Ve E-Öğrenmeye Yönelik Tutumlarının Farklı Değişkenler Açısından İncelenmesi. Dokuz Eylül Üniversitesi Eğitim Bilimleri Enstitüsü Bilgisayar Ve Öğretim Teknolojileri Eğitimi Anabilim Dalı Bilgisayar Ve Öğretim Teknolojileri Öğretmenliği Programı. Yüksek Lisans Tezi, 2012.

Experimental and Applied Medical Science, 3,3: 395-402, 2022. DOI 10.46871/eams.2022.45

Sectionary Analysis Of Thyroid Function Tests, Vitamin B12 And Folic Acid Levels In Patients With Type 2 Diabetes Mellitus, Hypertension, Chronic Renal Disease And Gastroesophageal Reflux Disease

Hamit Yildiz[1], Deniz Yildiz Pehlivan[2]

[1]Gaziantep University, Faculty of Medicine, Dep. of Internal Medicine, Gaziantep, Turkey.

[2]İzmir Kâtip Çelebi University, Faculty of Medicine, Dep. of Physiology, İzmir, Turkey

Abstract

The most common diseases presenting to the internal medicine outpatient clinic are type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease. Thyroid function tests, vitamin B12 and folic acid levels were compared in these diseases. Within the scope of the study, 91 patients were included in the study. Cases with type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease as chronic diseases were examined in the study. In this context, besides demographic data and routine biochemical data, TSH, fT3, fT4, vitamin B12 and folic acid levels were also scanned retrospectively from patient files. The mean age of the 91 patients included in the study was 61.29 ± 14.23 and was not statistically different between the groups. The FT3 level was found to be the highest in the first group compared to the other groups, but it was not statistically significant (p=0.863). The highest FT4 level was detected in group 4, but it was not statistically significant (p=0.839). TSH value was found to be the highest in the gastroesophageal reflux disease group and was not statistically significant when compared to other groups (p=0.898). The comparison of folic acid and vitamin B12 levels between the groups was not statistically significant (p=0.605). Spearmens's correlation analysis revealed folic acid was significantly positive correlated with folic acid (rho=0.797, p=0.001). TSH levels were not significantly corelated with fT3, fT4, folic acid and vitamin B12 (rho=0.015, p=0.891; rho= -0.177, p=0.093; rho=0.011, p=0.916; rho=0.153, p=0.147). This study demonstrated that serum TSH, ft3, ft4, vitamin b12 and folic acid levels were found similar in all groups. On the other hand, significant difference was not found between groups in term of TSH, fT3, fT4, vitamin B12 and folic acid.

Keywords: *Type 2 diabetes mellitus, hypertension, chronic renal diseas, gastroesophageal reflux disease*

***Corresponding Author:** Dr. Hamit Yıldız, e-mail: drhyildiz@hotmail.com, ORCID ID:0000-0001-7858-5123.

Introduction

Patients applying to the internal medicine outpatient clinic are divided into two groups as acute and chronic diseases. Important chronic diseases in the field of internal medicine are diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux disease causing dyspepsia.

Type 2 diabetes mellitus accounts for more than 90 percent of diabetes cases in the United Statesand Europe. Type 1 diabetes has a share of 5-10%. Genetic and environmental factors play a rolein the pathogenesis of diabetes mellitus. In addition, various phenotypic forms of diabetes, defined as "atypical diabetes", which do not fully comply with the definitions of type 1 and type2 and whose pathogenesis has not been fully elucidated, are emerging. Weight gain due to inactivity and obesity, which are a worldwide problem, also increase the incidence of type 2 diabetes. Type 2 diabetes is the most common phenotypic form of diabetes in adults, andhyperglycemia is characterized by varying degrees of insulin resistance and deficiency. Insulin resistance and insulin deficiency may occur with genetic and environmental effects, which may impair beta cell function in every patient and may make insulin resistance known as glucotoxicity more evident (1,2).

Hypertension has a high prevalence worldwide, and hypertension prescriptions among non- pregnant adults in the United States are a major cause of hospital visits and chronic prescription drug use (3,4).

In addition, blood pressure control is not sufficient in approximately half of the patients with hypertension. However, patients do not apply to health professionals because they do not have obvious symptoms. The prevalence of hypertension in the United States is higher in men, older adults, black adults, and rural individuals (5,7). The global prevalence of hypertension is similar to that in the United States, although it varies by country (8). Pooled data using the definition of hypertension as taking antihypertensive medication or having systolic
≥140 mmHg or ≥90 mmHg diastolic blood pressure show that in 1990 approximately 32 percent of the world's adult population (aged 30 to 79 years) had hypertension (9).

Chronic kidney disease is the name given to irreversible deterioration of kidney function. Chronic kidney disease guidelines state the concept of kidney disease, which requires the attention of general internists, to develop strategies for its early detection and management. Chronic kidney failure, regardless of the cause. It is defined as the presence of kidney damage or decreased kidney function for one or more months (10). Damage or diminished function must persist for at least 3 months. Decreased kidney function usually refers to a decreased glomerular filtration rate (GFR) estimated using serum creatinine and one of the existing equations (eGFR).

The passage of gastric contents through the esophagus is a normal physiological process. Gastroesophageal reflux is defined as a disease when it causes macroscopic damage to the esophagus or causes symptoms. Patients presenting to general internal medicine outpatient clinics describe symptoms that are independent of each other. For this reason, many diseases should be considered in the differential diagnosis and appropriate diagnostic tests should be requested. Thyroid dysfunction, iron deficiency anemia, vitamin B12 deficiency and folic acid deficiency should also be considered in the differential diagnosis of weakness and fatigue, which are two important complaints seen in internal medicine outpatient clinics. In this study, the frequency of possible accompanying thyroid dysfunction and other causes of anemia in patients diagnosed with type 2 diabetes mellitus, hypertension, chronic kidney disease and gastroesophageal reflux were investigated.

Materials and methods

Study groups

315 patients who applied to the internal medicine outpatient clinic were included in the study. Acute diseases were not included in the evaluation. The patients were evaluated in terms of chronic disease. Among the chronic diseases, hypertension was defined as type 2 diabetes mellitus, chronic kidney disease and gastroesophageal reflux. 91 patients with chronic disease were included in the study. Exclusion criteria for the study were type 2 diabetes mellitus, chronic kidney disease, hypertension, and having a chronic disease other than gastroesophageal reflux. Demographic, clinical and laboratory data of the patients were collected retrospectively from patient files. Glucose, urea, creatinine, uric acid, albumin, globulin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, lactate used in the study. The standart reference ranges were as follows: fT4 0.61-1.45 ng/dL, fT3 2,5-3,9 ng/dL, vitamin B12 180-914 ng/L, and folic acid 5.9-24.8 ug/L. Dehydrogenase, total bilirubin, calcium, phosphorus, vitamin B12, folic acid, thyroid stimulating hormone, free T3 and free T4 levels were obtained retrospectively. The diagnoses of the patients were diagnosed using the diagnostic criteria determined by the international guidelines, or the patients who were previously diagnosed and using active treatment were considered to have a previous diagnosis. The study protocol was made with the permission of Gaziantep University ethics committee.

Statistical analysis

In the present study, compliance of variables with normal distribution have been evaluated using histograms, variation coefficients, skewness, sharpness, detrended normality graph and Kolmogorov–Smirnov test. Median (minimum/maximum) has been used to present descriptive statistics of variables without normal distribution. Mean standard deviation (SD) values ofvariables with normal distribution are

provided (mean ± SD, 95% CI). ANOVA test has been used to evaluate differences between groups in terms of fT3, fT4,TSH, vitamin B12, and folic acid. When the ANOVA test was applied, no statistically significant difference could be detected between the variances, so post hoc analysis was not needed and was not used. The Pearson correlation test has been used for continuous variables that showed a normal distribution. IBM SPSS version 24 (IBM Corp., Armonk NY, USA) have been used for statistical analysis and calculations. Statistical significance level has been defined as $P < 0.05$.

Results

The mean age of the patients was 61.29 ±14.23. 49.5% (n:45) of the patients were female and 48.4% (n:46) were male. Biochemical and hormonal parameters of the entire study population are given in the table. The patients were divided into groups according to the main diagnostic groups. The first group consists of hypertension, the second group consists of type 2 diabetes mellitus, the third group consists of chronic kidney disease and the fourth group consists of gastroesophageal reflux disease. The first group consisted of 30 patients with hypertension, the second group consisted of 39 patients with type 2 diabetes mellitus, the third group consisted of 20 patients with chronic kidney disease, and the fourth group consisted of 2 patients with gastroesophageal reflux. According to the groups, the values of the biochemical parameters of the patients at the time of application are given in the table. Among the patients included in the study, the rate of smokers in the 1st group was 18.5%, 15.7% in the 2nd group, 14.8% in the 3rd group and 13.97% in the 4th group. There was no statistically significant difference in terms of body mass index (BMI) of the patients (p=0.672). The FT3 level was found to be the highest in the first group compared to the other groups, but it was not statistically significant (p=0.863). The highest FT4 level was detected in group 4, but it was not statistically significant (p=0.839). TSH value was found to be the highest in the gastroesophageal reflux disease group and was not statistically significant when compared to other groups (p=0.898). The comparison of folic acid and vitamin B12 levels between the groups was not statistically significant (p=0.605).

It was performed Spearmen's correlation analysis to evaluate the associations between serum TSH, fT3,fT4, folic acid and Vitamin B12. Spearmens's correlation analysis revealed folic acid was significantly positive correlated with folic acid (rho=0.797, p=0.001). TSH levels were not significantly corelated with fT3, fT4, folic acid and vitamin B12 (rho=0.015, p=0.891; rho= - 0.177, p=0.093; rho=0.011, p=0.916; rho=0.153, p=0.147). FT3 was positively correlated with TSH and folic acid (rho=0.015, p=0.891; rho=0.797, p=0.001) and negative correlated with fT4 and vitamin B12 (rho= -0.040, p=0.709; rho= -0.109, p=0.309). FT4 was positively correlated with vitamin B12 (rho=0.022, p=0.837 and negative correlated with TSH, fT3, vitamin B12

and folic acid (rho= -0.177, p=0.093; rho= -0.040, p= -0.030; rho=0.776). Vitamin B12 was positively correlated with TSH, fT4 and folic acid (rho=0.153, p=0.147; rho=0.022, p=0.837; rho= 0.056, p=0.601) and negative correlated with fT3 (rho= -0.109, p=0.309). Folic acid was positively correlated with TSH, fT3 and vitamin B12 (rho=0.011,p=0.916; rho=0.767,p=0.01; rho=0.056, p=0.601).

Table 1. The clinical characteristics of all patients

	Mean± Standart deviation
Glucose (mg/dL)	162.40 ± 68.82
Urea(mg/dL)	83.74 ± 62.22
Urıc acid(mg/dL)	7.19 ±3.94
Creatinine(mg/dL)	1.44 ±1.43
Albumin (g/dL)	3.20 ±1.90
Globulin (g/dL)	3.04 ±0.83
Total protein (g/L)	11.50 ±52.11
AST (U/L)	197.02 ±487.10
ALT(U/L)	108.97 ±285.18
ALP(U/L)	179.08 ± 182.94
GGT(U/L)	136.60 ±195.23
Total Bilirubin(mg/dL)	1.24 ±2.33
LDH (U/L)	390.40 ±165.87
Calcium(mg/dL)	8.44 ±1.40
Phosphorus(mg/dL)	4.60 ±1.96
Vitamin B12(pg/mL)	575.97 ±442.46
Folic acid(ng/mL)	8.48 ±7.43
TSH(mU/L)	2.67 ±6.19
fT3 (pg/mL)	6.01 ±23.04
fT4(pg/mL)	1.22 ±0.64

Table 2 The clinical characteristics of all patients separated by groups

		Mean ±Standart deviation	95% CI (Lower-Upper)	*p*
Free T3				
	1.Group	8.03 ± 28.68	-2.88 - 18.93	
	2.Group	6.50 ± 25.08	-1.74 - 14.74	0.863
	3.Group	2.47 ± 0.53	2.23 - 2.72	
	4.Group	2.36 ± 0.61	-3.10 - 7.82	
Free T4				
	1.Group	1.24±0.811	0.94 - 1.54	
	2.Group	1.23±0.64	1.02 - 1.44	
	3.Group	1.12±0.28	0.99 - 1.25	0.839
	4.Group	1.37±0.70	-4.98 - 7.72	
TSH				
	1.Group	2.09±2.86	1.02 - 3.16	
	2.Group	3.30±8.78	0.45 - 6.15	
	3.Group	2.16±3.47	0.54 - 3.79	0.898
	4.Group	3.79±4.89	-40.23 - 47.80	
Folic acid				
	1.Group	8.85±8.34	1.52 - 5.74	
	2.Group	8.81±8.18	1.31 - 6.16	
	3.Group	7.48±4.47	0.99 - 5.39	0.882
	4.Group	6.36±0.29	3.69 - 9.03	
Vitamin B12				
	1.Group	602.00±469.14	426.82 - 777.18	
	2.Group	524.85±417.54	389,50 - 660.19	
	3.Group	659.60±469.92	439.67 - 879.53	0.605
	4.Group	346.00±219.20	-1623.46 - 2315.46	

Table 3 Perason's correlation analysis between laboratory variables and clinical features for patients

	TSH	**fT3**	**fT4**	**Vitamin B12**	**Folic acid**
TSH					
rho	1	0.015	-0.177	0.153	0.011
p		0.891	0.093	0.147	0.916
fT3					
rho	0.015	1	-0.040	-0.109	0.797
p	0.891		0.709	0.309	0.001
fT4					
rho	-0.177	-0.040	1	0.022	-0.030
p	0.093	0.709		0.837	0.776
Vitamin B12					
rho	0.153	-0.109	0.022	1	0.056
p	0.147	0.309	0.837		0.601
Folic acid					
rho	0.011	0.767	-0.030	0.056	1
p	0.916	0.001	0.776	0.601	

Discussion

In the present study, it is found that the serum levels of vitamin B12, folic acid, TSH, free T3 and free T4 were not statistically different between patients groups but the levels of these parameters were found insignificantly different in terms of groups. The highest TSH value, the lowest folic acid and vitamin B12 levels were found in the gastroesophageal reflux disease group. This indicates that patients with gastroesophageal reflux disease should use acid-suppressing therapy, which is an important goal of treatment. It is known that the bioavailability of levothyroxine preparations used in the treatment of hypothyroidism is also low due to drug interactions, and it shows that acid suppressive treatments cause an increase in TSH level for this reason. These results are important evidence that the treatment of patients with gastroesophageal reflux disease differs in some hormone and vitamin parameters, which are the basic needs of the body.

The prevalence of gastroesophageal reflux disease is increasing worldwide and causes deterioration in quality of life (11,12). Dyspepsia is a disease characterized by abdominal pain, retrosternal pain, belching, bloating, and nausea, usually originating from the upper gastrointestinal tract. Reflux symptoms such as heartburn and regurgitation are considered typical symptoms of gastroesophageal reflux disease. However, other dyspeptic complaints may be seen in patients with non-erosive gastroesophageal reflux disease (13,14).

In the pathogenesis of dyspeptic patients, increased gastric acidity is treated by suppressing it with acid-suppressing drugs. In these patients, different clinical symptoms may accompany due to multiple pathogenesis of endocrine disorders. Hormonal interactions between systems are not clearly known. Gastrointestinal symptoms or signs may also cause thyroid disease symptoms to occur and, if ignored, may lead to misdiagnosis or delay in diagnosis (15).

Acid-suppressing treatments used in the treatment of reflux are proton pump inhibitors and histamine 2 receptor antagonists. These drugs are defined as acid-suppressing therapies (ALA) and are commonly used drugs for the gastrointestinal tract. Although the use of ALA is generally considered a safe therapeutic agent, long-term use of ALA raises concerns about vitamin B12 deficiency. The hypothesis of this situation can be explained by understanding how vitamin B12 is obtained in the human body. Diet is the only source of vitamin B12 for humans. Vitamin B12 is naturally protein bound. The human body uses stomach acid and pepsin to convert the vitamin to free vitamin B12, which then binds to the R-protein in the stomach. Once it reaches the less acidic duodenum, vitamin B12 is released from the R-proteins by pancreatic enzymes and binds to intrinsic factor. Vitamin B12 bound to intrinsic factor is then absorbed into the body via terminal ileum cubilin receptors (16,17). There are 2 reasons why chronic ALA use can cause vitamin B12 deficiency.

First, it inhibits the absorption of vitamin B12 by lowering stomach acidity. Vitamin B12 cannot be separated from dietary protein. Secondly, a higher pH value in the intestine may cause malabsorption by causing bacterial growth (18,19).

Levothyroxine, which is used in the treatment of thyroid, changes its absorption in case of increased gastric acidity (20). Various studies have confirmed that patients with impaired gastric acid secretion due to disease or using proton pump inhibitors may require higher doses of levothyroxine to achieve targeted TSH(21,22). This effect proves clinically important in patients with chronic ALA administration (23). Although the proton pump inhibitors pantoprazole and esomeprazole do not seem to change the pharmacokinetic parameters of levothyroxine, the data are insufficient to prove their safety (23,24).

References

1. Chiang JL, Kirkman MS, Laffel LM, et al. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014; 37:2034.
2. Purnell JQ, Dev RK, Steffes MW, et al. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. Diabetes 2003; 52:2623.
3. Muntner P, Carey RM, Gidding S, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation 2018; 137:109.
4. Yoon SS, Gu Q, Nwankwo T, et al. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. Hypertension 2015; 65:54.
5. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from theThird National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995; 25:305.
6. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003; 290:199.
7. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension,1988-2008. JAMA 2010; 303:2043.
8. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Hypertension1995; 26:60.
9. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104million participants. Lancet 2021; 398:957.
10. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011) 2013; 3:19.
11. P. Sharma, S. Wani, Y. Romero, D. Johnson, and F. Hamilton, “Racial and geographic issues in gastroesophageal reflux disease,” American Journal of Gastroenterology, vol. 103, no. 11, pp. 2669–2680,2008.
12. I. Wiklund, “Review of the quality of life and burden of illness in gastroesophageal reflux disease,” DigestiveDiseases, vol. 22, no. 2, pp. 108–114, 2004.
13. E. M. Quigley, “Review article: gastric emptying in functional gastrointestinal disorders,” AlimentaryPharmacology and Therapeutics, vol. 20, supplement 7, pp. 56–60, 2004.
14. G. Shi, S. Bruley des Varannes, C. Scarpignato, M. Le Rhun, and J.-P. Galmiche, “Reflux related symptoms in patients with normal oesophageal exposure to acid,” Gut, vol. 37, no. 4, pp. 457–464, 1995.
15. H. Noto, T. Mitsuhashi, S. Ishibashi, and S. Kimura, “Hyperthyroidism presenting as dysphagia,” InternalMedicine, vol. 39, no. 6, pp. 472–473, 2000.
16. Howden CW. Vitamin B12 levels during prolonged treatment with proton pump inhibitors. J Clin Gastroenterol2000; 30: 29–

33

17. Lachner C, Steinle NI, Regenold WT. The neuropsychiatry of vitamin B12 deficiency in elderly patients. J Neuropsychiatry Clin Neurosci 2012; 24: 5–15.

18. Kapadia C. Cobalamin (vitamin B12) Deficiency: Is it a Problem for Our Aging Population and Is the ProblemCompounded by Drugs That Inhibit Gastric Acid Secretion? New Haven (CT): Yale University School of Medicine; 2000; 4–6.

19. Abraham NS. Proton pump inhibitors: potential adverse effects. Curr Opin Gastroenterol 2012; 28: 615–20.

20. Ianiro, G.; Mangiola, F.; Di Rienzo, T.A.; Bibbò, S.; Franceschi, F.; Greco, A.V.; Gasbarrini, A. Levothyroxineabsorption in health and disease, and new therapeutic perspectives. Eur. Rev. Med. Pharmacol. Sci. 2014, 18, 451–456.

21. Sachmechi, I.; Reich, D.M.; Aninyei, M.; Wibowo, F.; Gupta, G.; Kim, P.J. Effect of proton pump inhibitors onserum thyroidstimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. Endocr. Pract. 2007, 13, 345–349. [CrossRef]

22. Irving, S.A.; Vadiveloo, T.; Leese, G.P. Drugs that interact with levothyroxine: An observational study from theThyroid Epidemiology, Audit and Research Study (TEARS). Clin. Endocrinol. 2015, 82, 136–141.

23. Pa´sko, P.; Wołtosz, A.; Zwoli ´nska-Wcisło, M.; Zachwieja, Z. Influence of proton pump inhibitors on calciumand iron homeostasis. Bromatol. Chem. Toksykol. 2015, 48, 484–489.

24. Dietrich, J.W.; Boehm, B.O. Thyroxine in goiter, H. pylori infection, and gastritis. N. Engl. J. Med. 2006, 355,1177

25. Ananthakrishnan, S.; Braverman, L.E.; Levin, R.M.; Magnani, B.; Pearce, E.N. The effect of famotidine,esomeprazole, and ezetimibe on levothyroxine absorption. Thyroid 2008, 18, 493–498.

Experimental and Applied Medical Science, 3,3: 410-419, 2022. DOI 10.46871/eams.2022.47

May Neutrophil Lymphocyte Ratio Be A Predictor of Neuropathy in Diabetic Patients?

Hamit Yıldız[1], Deniz Yıldız Pehlivan[2]

[1]Gaziantep University, Faculty of Medicine, Department of Internal Medicine, Gaziantep, Turkey.

[2]İzmir Kâtip Çelebi University, Faculty of Medicine, Department of Physiology, İzmir, Turkey

Abstract

It is known that there are immunological inflammatory mechanisms that play a role in the pathogenesis of type 2 diabetes mellitus (DM), which is a common metabolic disease in adults. Chronic inflammation plays a role in the development of chronic microvascular complications. Neutrophil-lymphocyte ratio (NLR) is a new marker of inflammation that is inexpensive and easy to administer. NLR is accepted as a marker of systemic inflammation and is used as a prognostic marker in patients with heart diseases and malignancies. The aim of this study is to examine whether there is a relationship between NLR and neuropathy, one of the microvascular complications, in patients with type 2 diabetes mellitus in adults. One hundred and nine diabetic patients (40 without microvascular complications and 69 with microvascular complications) were included in the study. Microvascular complications from DM were evaluated with NLR and compared with different inflammatory markers. NLR was higher in patients with diabetic complications compared to the group without (20.40±14.79 vs 5.56±3.46, respectively; p<0.001). Spearmens's correlation analysis revealed NLR was significantly positively correlated with ESR (r:0.633, p:<0.001) and CRP (r: 0.387, p:<0.001). Increased NLR levels may be associated with neuropathy in type 2 diabetic patients.

Keywords: *Type 2 diabetes mellitus, neutrophil lymphocyte ratio, neuropathy, microvascular complication*

***Corresponding Author:** Dr. Hamit Yıldız, e-mail: drhyildiz@hotmail.com, ORCID ID:0000-0001-7858-5123.

Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disease in adults. It is estimated that diabetes mellitus affects 537 million adults worldwide (1). In an analysis of data from the National Health Interview Survey (2016 and 2017), the prevalence of diagnosed type 2 diabetes among adults in the United States was 8.5 percent (2). The main reasons for the increase in prevalence are hypercaloric nutrition, obesity, decreased physical activity and secondary causes (3). DM is a chronic and metabolic disease characterized by high blood sugar levels that can lead to the development of acute, chronic microvascular and macrovascular complications. T2DM usually occurs due to insulin resistance and impaired insulin secretion. In 90% of T2DM patients, there is insufficient insulin secretion from pancreatic beta cells, insulin resistance in tissues, and insufficient compensatory insulin secretion response (4-5). Uncontrolled disease causes hyperglycemia, and the insulin secreted cannot maintain glucose homeostasis. Patients with T2DM are mostly obese or have increased adipose tissue predominantly in the abdomen. In this reduction, adipose tissue supports the development of insulin resistance through various inflammatory mechanisms, including increased free fatty acid (FFA) secretion and adipokine degranulation. In the development of T2DM, pancreas (alpha and beta cells), liver, skeletal muscles, kidneys, brain, small intestines and adipose tissue are affected together (6).

Data obtained from studies show that adipokine tissue dysregulation, inflammation, abnormalities in intestinal microbiota, and immune dysregulation are important factors that play a role in the pathogenesis of the disease (7).

In the case of physical inactivity, which is an important cause of diabetes, glucose uptake into tissues and insulin sensitivity are reduced. Furthermore sedentary life causes inflammation and oxidative stress at the tissue level, which are predisposing factors for T2DM (8). Oxidative stress plays a role in the pathogenesis of many rheumatic diseases besides diabetes mellitus (9-13). Many studies support that chronic moderate inflammation may be associated with insulin resistance and the development of complications (14-16). Studies correlate leukocyte count (WBC) and C-reactive protein (CRP) with diabetes-related microvascular and macrovascular complications (17-18). Blood neutrophil lymphocyte ratio (NLR) is a new marker that shows the body's total inflammation level because it is an inexpensive, easy, and effective marker of subclinical inflammation. NLR has been shown to be an indicator of inflammation and prognostic features in many diseases (19-20). In fact, it is stated that NLR is a better predictor marker than leukocyte count in some diseases (21-22). The aim of the current study is to determine the relationship between the level of NLR, a practical marker of inflammation, and neuropathy in patients with T2DM.

Materials and Methods

Patients who were referred to the clinic of Deparment of Internal Medicine, Division of General Medicine at Gaziantep University Hospital were included in this cross-sectional study.

All patients were questioned for history of DM (known diabetes treated with diet or drugs or both or either newly diagnosed according to the American Diabetes Association criteria (23).

The first indicator of diabetic nephropathy is microalbuminuria, which is defined as a 24-hour urine albumin level of 30-300 mg in the absence of urinary tract infection and/or uncontrolled hypertension (24). The diagnosis of diabetic neuropathy was defined according to the deterioration in nerve conduction work in patients with sensory impairment/motor weakness or polyradiculopathy (25). The diagnosis of retinopathy was defined as having at least microaneurysm and/or retinal hemorrhage and/or other retinal damage findings (26-27).

Laboratory data were obtained retrospectively from patient files. Complete blood count, fasting plasma glucose, uric acid, creatinine, albumin, globulin, total protein, aspartate amino transferase, alanine aminotransferase, total bilirubin, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase and hemoglobin A1c levels were measured with a hospital autoanalyzer. Complete blood count analysis was measured by Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer. NLR was calculated from differential count by dividing the absolute neutrophil count by the absolute lymphocyte count.

End-stage renal disease, malignant disease, advanced liver disease, presence of active infection and active smokers were excluded from the study. WBC counts more than 11.0 (x103 cells/mm3) and less than 4.0 (x103 cells/mm3) were exclusion criteria for the study.

Informes consent has been obtained, and procedures followed were in acccordance with the institutional ethical standars of the responsible commitee on human experimentation. The study protocol was approved by the Gaziantep University Local Research Ethics Committee.

Patients who were referred to the clinic of Deparment of Internal Medicine, Division of General Medicine at Gaziantep University Hospital were included in this cross-sectional study.

All patientes were questioned for history of DM (known diabetes treated with diet or drugs or both or either newly diagnosed according to the American Diabetes Association criteria(23).

Statistical Analysis

For the statistical analysis of the data, SPSS (Statistical Package for Social Sciences) 22.0 version statistical program was used. All data were entered into a database and were verified by a second independent person. The Shapiro-Wilk test was used to test whether the numerical variables were consistent with the normal

distribution. Paremeters with normal distribution have been evaluated using histograms, variation coefficients, skewness, sharpness, detrended normality graph and Kolmogorov–Smirnov test. Mean standard deviation (SD) values of variables with normal distribution are provided (mean ± SD). Categorical variables are shown as frequencies. Independent samples t-test was used to compare normally distributed variables in two groups. Correlation between ESR, CRP, and NLR was performed with Spearmen's correlation test. Statistical significance level has been defined as $P < 0.05$.

Results

The mean age of 109 patients with type 2 diabetes mellitus included in the study was 61.20± 13.87 years. The mean age of male patients was 61.25±14.50 and the mean age of femalepatients was 61.13±13.10. Demographic properties and laboratory parameters of the study are presented in Table 1. There was no significant difference between the diabetic patients withand without microvascular complications regarding of ESR and CRP.

Table 1. Demographic properties and laboratory parameters of the study populations.

Parameters	DM patients without complications (n:40)	DM patients with complications (n: 69)	***p***
Gender (n,%)			
Male	24 (%60)	39 (%56.5)	
Female	16 (%40)	30 (%43.5)	
Age (yr)	59.5±11.29	62.0±5.23	0.019
NLR	5.56±3.46	10.40±4.79	<0,001
Neutrophil (/mm^3)	6170±482	12010±930	0,019
Lymphocyte (/mm^3)	1275±123	730±66,5	0,002
Glucose (mg/dl)	124.5±62.83	147.10±72.1	0,208
Uric asid (mg/dl)	6.55±3.94	6.10±3.87	0.504
Creatinine (mg/dl)	0.88±1.11	0.80±1.55	0.253
Albumin (g/dl)	2.55±0.52	2.90±2.15	0.273
Globuline (g/dl)	3.03±0.90	3.00±0.79	0.242
Total Protein (g/dl)	6.05±1.09	6.10±5.98	0.149
AST (U/l)	35±5.24	47±54	0.966
ALT (U/l)	22±3.22	29±32	0.978
ALP (U/l)	114±18.4	27±17.1	0.667
GGT (U/l)	56.5±2.29	65±18.4	0.472
Total bilirubin(mg/dl)	0.60±2.29	0.60±1.62	0.087
LDH (U/l)	297±16.8	368±160.4	0.723
WBC (/mm^3)	8470±648	9060±1017	0.123
Hgb (g/dl)	12.78±2.47	12.90±2.34	0.909

Plt (/mm^3)	152500±14850	216000±15166	0.986
Duration of DM	8.37±3.75	6,15±3,18	0.089
HbA1c (%)	6.96±0.44	8,80±1,44	<0,001

DM: diabetes mellitus; NLR: neutrophil/lymphocyte ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gama glutamile transferase; LDH: lactat dehydrogenase; HGB: hemoglobin; WBC: White blood cell; Plt: platelet; HbA1c: glycated hemoglobin

All patients (n:69) with microvascular complications had neuropathy. Of the 69 patients with neuropathy, 21 also had nephropathy and 18 had retinopathy. There were 69 patients with defined microvascular complications. The mean of NLR of patients with microvascular complication was significantly higher than diabetic patients without complications (10.40±4.79 and 5.56±3.46 ,respectively). The NLR of patients id shown in figure 1. NLR was

higher in diabetic patients with nephropathy, neuropathy and retinopathy than in diabetic patients without any of these complications (p:0.021 , p:0.042, and p:0.007, respectively).

There was statistically significant positive correlation between NLR and ESR levels (r: 0.633, p:<0.001). In addition NLR was also positively correlated with CRP levels (r: 0.387, p:<0.001). Correlation analysis results between inflammatory indices are shown in Table 3.

Table 2. NLR of diabetic patients with microvascular complications.

		Mean ± SD	P
Microvascular complications (n:69)	(+)	20.41 ±14.79	<0.001
	(-)	5.57 ± 346	
Nephropathy (n:21)	(+)	14.05 ±14.29	0.267
	(-)	15.89 ±13.60	
Neuropathy (n:69)	(+)	20.40 ±14.79	<0.01
	(-)	5.57 ±3.46	
Retinopathy (n: 18)	(+)	15.02±14.34	0.802
	(-)	14.90±13.61	

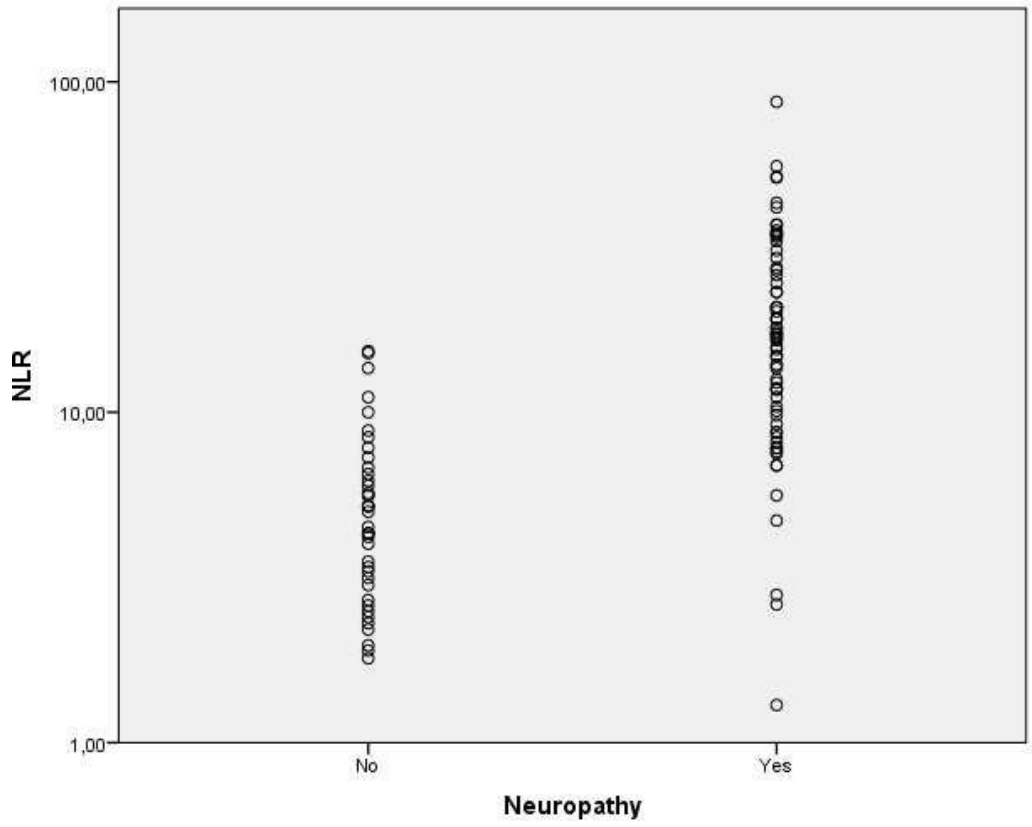
NLR: Neutrophil/lymphocyte ratio

Table 3. Correlation analysis results of inflammatory indices.

Parameters		
NLR-ESR	p: <0.001	r: 0.633
NLR-CRP	p:<0.001	r: 0.387
ESR-CRP	P:<0.001	r: 0.590

NLR: neutrophil/lymphocyte ratio; CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

Figure 1- Relationship between neutrophil lymphocyte ratio and diabetic neuropathy



Discussion

The present study aimed to investigate the relationship of NLR, an innovative marker of inflammation, in the presence of microvascular complications in patients with type 2 diabetes mellitus. It was aimed to detect a noninvasive marker of neuropathy, one of the microvascular complications. Study data revealed that diabetic patients with neuropathy from microvascular complications had higher NLR levels than individuals without neuropathy. In addition, NLR levels were found to be higher in patients with other microvascular complications than in patients with type 2 diabetes mellitus without complications.

Increased free oxygen radicals and decreased antioxidant substances are blamed for the development of macrovascular and microvascular complications related to type 1 and 2 diabetes mellitus (28). It is not known exactly which oxidative stress mechanism causes the development of diabetic complications. Diabetes damage can be thought of as the oxidative damage effects of chronic hyperglycemia in tissues.

Increased intracellular glucose causes the formation of higher oxidative stress molecules than antioxidant systems can buffer. These oxidative molecules cause the activation of protein kinase C (PKC), oxidative stress molecules induced by hyperglycemia, increased hexosamine pathway flux, increased AGEs and increased polyol pathway flux. In particular, activation of the AGEs pathway can damage cells that regulate gene transcription and proteins between the matrix and other tissues.

An important detoxification system of the body, which plays a critical role in defending thiol/disulfide homeostasis, the importance of which has been better understood in recent years, covers all groups in the acute and chronic inflammatory filters (29)). The thiol (-SH) is composed of hydrogen and sulfur atoms containing a sulphidhydryl group. Thiols can bind to oxidative molecules due to the presence of -SH groups that are sensitive to oxidation. Disulfides (-S-S-) are an important class of redox-reactive molecules occurring between thiol groups. Dynamic thiol-disulfide homeostasis is the reversal of the oxidative effect of proteins in our body caused by thiols. It is an important parameter associated with many biochemical processes, including regulation of protein function, stabilization of protein structure, protection of proteins against irreversible oxidation of cysteine residues, chaperone function, regulation of enzyme functions, and transcription (30). Increased oxidative stress as a result of zinc deficiency has been associated with inflammatory diseases (31-32). Zinc in the islet cells of the pancreas is important for the synthesis, storage and secretion of insulin. It is known that large amounts of zinc are excreted from the body in diabetic conditions. Zinc deficiency and increased oxidative stress have an important effect on the pathogenesis of diabetic complications (33).

Studies in the literature show that chronic inflammation plays a role in the pathogenesis of diabetes mellitus (34). In patients with T2DM, inflammatory markers can cause hyperglycemia with insulin resistance and beta cell dysfunction (35). Inflammation alters

endothelial function and causes a decrease in nitric oxide and prostacyclin production in the vascular endothelium (36). Widespread endothelial damage and overexpression of some mediators may lead to the development of diabetic complications. CRP, interleukin 6, and increased WBC levels have been associated with T2DM in some studies. In a meta-analysis, it was revealed that the

risk of diabetes is higher in patients with high CRp levels (37). In addition, it has been shown that there is a positive relationship between interleukin 6 level and new-onset diabetes mellitus due to obesity and insulin resistance (38).

Blood NLR is a simple, inexpensive, easy-to-access, low-cost, and non-invasive marker of systemic inflammation that can be obtained from complete blood count. This marker is used to determine prognosis in cardiovascular diseases, malignancies and inflammatory diseases. High NLR is associated with poor prognosis in esophageal, hepatocellular, epithelial ovarian, and nasopharyngeal cancers (39). Recent studies show that it is a strong indicator for predicting cardiovascular outcomes in patients with coronary artery disease (40-41).

The data of this study underline that NLR may indicate a systemic inflammatory state in diabetes mellitus-related complications. In addition, the data obtained within the scope of the study suggest that NLR can be used as an easy and inexpensive test for the early diagnosis of diabetic neuropathy and other microvascular complications. Comprehensive studies with prospective, repetitive NLR measurements will be useful in elucidating the pathogenesis of neuropathy, a microvascular complication in patients with T2DM.

References

1. IDF Diabetes Atlas 2021, 10th edition https://diabetesatlas.org/atlas/tenth-edition/ (Accessed on January 17,2022).
2. Xu G, Liu B, Sun Y, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. BMJ 2018; 362:k1497.
3. Chatterjee, S.; Khunti, K.; Davies, M.J. Type 2 diabetes. Lancet 2017, 389, 2239–2251.) (NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016, 387, 1513–1530.
4. Stumvoll, M.; Goldstein, B.J.; van Haeften, T.W. Type 2 diabetes: Principles of pathogenesis and therapy. Lancet 2005, 365, 1333–1346.
5. Weyer, C.; Bogardus, C.; Mott, D.M.; Pratley, R.E. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J. Clin. Investig. 1999, 104, 787–794.
6. Defronzo, R.A. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009, 58, 773–795.
7. Schwartz, S.S.; Epstein, S.; Corkey, B.E.; Grant, S.F.; Gavin, J.R., 3rd; Aguilar, R.B. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the beta-Cell-Centric Classification Schema. Diabetes Care 2016, 39, 179–186.
8. Strasser, B. Physical activity in obesity and metabolic syndrome. Ann. N. Y. Acad. Sci. 2013, 1281, 141– 159.
9. Koca I, Tutoglu A, Boyacı A, Pehlivan Y, Yıldız H, Turkbeyler I, Sarıcicek E, Taysi S, Onat AM. An evaluation of oxidative stress and antioxidant capacity in patients with myofascial pain syndrome. Mod Rheumatol. 2014 Nov;24(6):992-6. doi: 10.3109/14397595.2014.886984. Epub 2014 Mar 26. PMID:24670130.
10. Zengin O, Onder ME, Sarica MA, Turkbeyler IH, Kimyon G, Demir ZH, Yildiz H, Kisacik B, Onat AM. Systemic vasculitis in a patient with rhupus syndrome. Reumatismo. 2015 Dec 23;67(4):161-4. doi: 10.4081/reumatismo.2015.858. PMID: 2721518.
11. Apaydın Z. , Yıldız H. , Samin F. , Alaşehirli B. Investigation of Dynamic Thiol Disulfide Homeostasis in Acute Respiratory Failure Patients in Intensive Care Unit. Experimental and Applied Medical Science. 2021;2(2): 164-175.
12. Yıldız H, Yıldız Pehlivan D. Analysıs of thıole/dısulfide homeostasıs ın patıents wıth decubıtus ulcer. Experimental and Applied Medical Science. 2022; 3(2): 345-353.
13. Yildiz H. Successful therapeutic hypothermia in a propofol-related cardiac arrest case: a case report and literature review. Ther Hypothermia Temp Manag. 2018 Dec;8(4):239-244. doi: 10.1089/ther.2018.0009. Epub 2018 Jul 11. PMID: 29993335.
14. Pradhan AD, Cook NR, Buring JE, Manson JE, Ridker PM. C-reactive protein is independently associated with fasting insulin in nondiabetic women. Arterioscler Thromb Vasc Biol 2003, 23: 650-5.
15. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006, 116: 1793-801. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratiopredicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. Ann Surg Oncol 2009, 16: 614-22.
16. Yildiz H. The relationship between neutrophil lymphocyte ratio and 28-day mortality in intensive care patients. Progr Nutr [Internet]. 2019 Sep. 18 [cited 2022 Dec. 15];21(3):566-9. Available from: https://www.mattioli1885journals.com/index.php/progressinnutrition/article/view/8720.
17. Zahorec R. Ratio of neutrophil to lymphocyte counts - rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001, 102: 5-14.
18. Bhutta H, Agha R, Wong J, Tang TY, Wilson YG, Walsh SR. Neutrophil-lymphocyte ratio predicts medium- term survival following elective major vascular surgery: a cross-sectional study. Vasc Endovascular Surg 2011, 45: 227-31.
19. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010 Jan;33 Suppl 1(Suppl 1): S62-9. doi: 10.2337/dc10-S062. Erratum

in: Diabetes Care. 2010 Apr;33(4): e57. PMID: 20042775; PMCID: PMC2797383.

20. Farag YM, Al Wakeel JS. Diabetic nephropathy in the arab gulf countries. Nephron Clin Pract 2011, 119:c317-22.

21. Ko SH, Cha BY. Diabetic peripheral neuropathy in type 2 diabetes mellitus in Korea. Diabetes Metab J 2012,36: 6-12.

22. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care 2003, 26: 226-9.

23. Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology 2011, 16: 86-9.

24. Bashan N, Kovsan J, Kachko I, Ovadia H, Rudich A. Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. Physiol Rev. 2009;89(1):27–71.

25. Yildiz H. Thiol/disulphide homeostasis in intensive care unit patients with sepsis and septic shock. Turk J Med Sci. 2020 Jun 23;50(4):811-816. doi: 10.3906/sag-1905-148. PMID: 32233178; PMCID: PMC7379464.

26. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci. 2020 Nov 3;50(SI-2):1728-1738. doi: 10.3906/sag-2003-64. PMID: 32233181; PMCID: PMC7672356.

27. Tudor R, Zalewski PD, Ratnaike RN. Zinc in health and chronic disease. J Nutr Health Aging. 2005;9(1):45-51. PMID: 15750665.

28. Yildiz H. Is it given over importance to serum zinc level in patients with sepsis? Zinc and sepsis. Progr Nutr [Internet]. 2019 Sep. 18 [cited 2022 Dec. 15];21(3):605-10. Available from: https://www.mattioli1885journals.com/index.php/progressinnutrition/article/view/8672.

29. Barman S, Srinivasan K. Diabetes and zinc dyshomeostasis: Can zinc supplementation mitigate diabetic complications? Crit Rev Food Sci Nutr. 2022;62(4):1046-1061. doi: 10.1080/10408398.2020.1833178. Epub 2020 Oct 14. PMID: 33938330.

30. Pitsavos C, Tampourlou M, Panagiotakos DB, et al. Association between low-grade systemic inflammation and type 2 diabetes mellitus among men and women from the ATTICA Study. Rev Diabet Stud 2007, 4: 98-104.

31. Sattar N. Biomarkers for diabetes prediction, pathogenesis or pharmacotherapy guidance? Past, present and future possibilities. Diabet Med 2012, 29: 5-13.

32. Nakanishi N, Sato M, Shirai K, Suzuki K, Tatara K. White blood cell count as a risk factor for hypertension; a study of Japanese male office workers. J Hypertens 2002, 20: 851-7.

33. Dehghan A, Kardys I, de Maat MP, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. Diabetes 2007, 56: 872-8.

34. Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N. Adipokines and risk of type 2 diabetes in older men. Diabetes Care 2007, 30: 1200-5.

35. Öztürk ZA, Kuyumcu ME, Yesil Y, Savas E, Yıldız H, Kepekçi Y, Arıoğul S. Is there a link between neutrophil-lymphocyte ratio and microvascular complications in geriatric diabetic patients? J Endocrinol Invest. 2013 Sep;36(8):593-9. doi: 10.3275/8894. Epub 2013 Mar 19. PMID: 23511196.

36. Muhmmed Suliman MA, Bahnacy Juma AA, Ali Almadhani AA, Pathare AV, Alkindi SS, Uwe Werner F. Predictive value of neutrophil to lymphocyte ratio in outcomes of patients with acute coronary syndrome. Arch Med Res 2010, 41: 618-22.

37. Azab B, Zaher M, Weiserbs KF, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010, 106: 470-6.

Experimental and Applied Medical Science, 3,3: 420-429, 2022. DOI 10.46871/eams.2022.48

SARS-CoV-2 Infections in Vaccinated vs Unvaccinated Healthcare Workers: Assessment of the Effectiveness of CoronaVac

Hadiye Demirbakan[1], İpek Kocer[1], Aysen Bayram[1]
[1]Sanko University, Faculty of Medicine, Department of Medical/Clinical Microbiology

Abstract

Although several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been efficient against clinically significant coronavirus disease 2019 (COVID-19), breakthrough infections are being reported for several months. Here we conducted a prospective cohort study to assess the effectiveness of an inactive vaccine (CoronaVac; Sinovac, China) against SARS-CoV-2 by following cases of COVID-19 among vaccinated health care workers. Between March and September 2021, 1012 vaccinated and 211 unvaccinated healthcare workers from a tertiary care university hospital were followed for PCR-confirmed SARS-CoV-2 infections. COVID-19 active surveillance of the healthcare workers was carried out by the Infection Prevention and Control Unit of the institution. Anti-spike antibody values before and after COVID-19 were recorded. During a six-month follow-up program, in 35 out of 1012 (3.5%) fully vaccinated and in 16 out of 211 (7.6%) unvaccinated healthcare workers SARS-CoV-2 infections were documented. There was a statistically significant difference between vaccinated vs. unvaccinated workers regarding SARS-CoV-2 infections (P=0.003). Although all unvaccinated healthcare workers experienced symptomatic COVID-19, the vaccinated group suffered less from symptoms (100% vs. 77.1%, respectively; P=0.045). CoronaVac was 64.5% and 88.4% effective in preventing symptomatic and severe disease, respectively, and had an efficacy of 100% in preventing death among healthcare workers. In accordance with our findings, it was seen that CoronaVac could not prevent breakthrough infections, but was highly effective in preventing severe disease and death in healthcare workers for a period of six months after two consecutive doses.

Key words: SARS-CoV-2; COVID-19; CoronaVac; healthcare workers

Corresponding author: Asst. Prof. Dr. Hadiye Demirbakan, e-mail: hdemirbakan@sanko.edu.tr. ORCID ID.: 0000-0003-2764-3113.

Introduction

As of December 2019, COVID-19 disease caused by Severe Acute Respiratory SyndromeCoronavirus-2 (SARS-CoV-2) spread rapidly all over the world and was declared a pandemic by the World Health Organization (WHO) in March 2020 (1). In November 2021, it wasreported that there were more than 240 million cases of COVID-19 worldwide with more thanfive million deaths (2). Efforts towards the prevention of the pandemic have led to thedevelopment of several vaccines including inactivated vaccines, live virus vaccines,recombinant protein vaccines, vectored vaccines, and DNA or RNA vaccines (3, 4) Healthcare workers are in the high-risk group due to frequent exposure to SARS-CoV-2compared to other individuals during the pandemic. Emergency use approval was given for aninactivated COVID-19 vaccine (CoronaVac; Sinovac, China) as of January 2021 in Turkey andthe vaccine was administered as two doses 28 days apart, primarily to healthcare workers (5).CoronaVac induced %99.6 humoral immunity in healthcare workers 21 days after the seconddose, however data on the effectiveness of this vaccine for the prevention from COVID-19 arelimited (6).

In this study, the efficacy of CoronaVac was monitored over a six-month period in healthcare workers who received full-dose vaccination at a tertiary-care university hospital. During the same period of time, COVID-19 cases in healthcare workers who refused the vaccine were followed up. Symptomatic and asymptomatic SARS-CoV-2 infections confirmed via polymerase chain reaction (PCR) were evaluated in both vaccinated and unvaccinated healthcare workers.

Materials and Methods

Study Design

This was a prospective observational cohort study designed to estimate the association betweenvaccination with the CoronaVac vaccine and SARS-CoV-2 infections among health care workers. The study was carried out for a period of six months (24 weeks) between 15 March 2021, and 15 September 2021, at Sanko University Hospital, which is a tertiary-care teaching hospital, located in Gaziantep, southeastern part of Turkey staffed by about 1300 healthcare workers. Ethics approval was obtained from Institutional Clinical Research Ethics Committee (Date: 04.02.2021 Decision no: 01).

Participants

Healthcare workers who received two vaccine doses between January 14, 2021, and February 21, 2021, were assigned to the vaccinated group. The unvaccinated group was composed of health care workers who did not receive any doses of vaccine during this period. Study was started three weeks after all staff members had received a second dose of the vaccine. Participants in both groups were healthcare staff such as doctors, nurses, caregivers, medical technicians, laboratory staff, cleaning staff, students of medicine, academic and administrative staff. All participants were included in the study after completing the informed consent form. Demographic information and presence of chronic disease of the participants were recorded.

COVID-19 active surveillance of the

healthcare workers was carried out by the Infection Prevention and Control Unit of the institution. Routine controls of healthcare workers were managed by filling out the COVID-19 contact/case follow-up form and monitoring symptoms

such as fever, cough, cold, body aches, and fatigue weekly. Testing for the presence of SARS- CoV-2 by means of PCR assay remained readily available for fully vaccinated and unvaccinated staff who were symptomatic or had been exposed to an infected person, regardless of symptoms.

Vaccination Protocol

CoronaVac is an inactivated virus vaccine developed against SARS-CoV-2 infection (3). It is manufactured by Sinovac Life Sciences (Beijing, China) and is produced from a novel coronavirus (strain CZ02) grown in the kidney cell cultures (Vero Cell) of the African green monkey. The vaccine contains inactivated SARS-CoV-2 virus, aluminum hydroxide, disodiumhydrogen phosphate, sodium dihydrogen phosphate, and sodium chloride. Vaccinations of participants were performed intramuscularly to deltoid with the recommended dose of 0.5 mL containing 600 SU of SARS-CoV-2 virus antigen with interval of 28 days between the first and second doses. Status of vaccination of the healthcare workers was ascertained from the employee health database. Full vaccination was defined as more than 21 days after receipt of the second dose.

Antibody Detection

To record the vaccine-induced antibody response to SARS-CoV-2, serum samples were obtained three weeks after the second dose of CoronaVac in vaccinated group. Anti-spike antibody values were determined using the SARS-CoV-2 IGG Quant (Abbott, Ireland) kit in an immunoassay device (Abbott Architect i2000SR, USA) operating with the chemiluminescence method at the microbiology laboratory. In accordance with the recommendations of the manufacturer, the results were considered positive if they were greater than or equal to 50.0 AU/mL, and negative if they were below this value. Samples with values above 40,000AU/ml were analyzed after being diluted 1:2.

Diagnosis of COVID-19

The follow-up period for SARS-CoV-2 infection in both study groups was six months (24 weeks). In case of a symptomatic or asymptomatic suspected infection, the filiation process was initiated by the nurse of the Hospital's Infection Prevention and Control Unit. The diagnosis of COVID-19 was performed from nasopharyngeal and oropharyngeal swab samples via Coronagen RT-qPCR SARS-CoV-2 Variants Detection Kit (Gensutek, Turkey). Samples with a cycle threshold (Ct) value of <38 and sigmoidal curves were considered positive in line with the manufacturer's recommendation. PCR tests of the cases with negative results and continuing clinical suspicion were repeated with a new sample 24 hours later.

Participants infected with SARS-CoV-2 were defined as symptomatic if they had any of the following complaints: temperature > 37.2°C, flu-like symptoms such as headache, sore throat, cough, dyspnea, rhinorrhea, myalgia,

joint pain, malaise, and loss of sense of taste or smell.

Statistical Analysis

Mean and standard deviation or median and minimum-maximum values were given for the continuous variables as descriptive statistics, and frequency and percentage values were given for categorical variables. Chi-square test was used for group comparisons of categorical variables. $P < 0.05$ was considered statistically significant in all evaluations.

Results

The study group consisted of 1223 healthcare workers, out of which 1012 (82.7%) (age range, 18-69; mean [SD] age, 33.1 [10.8] years; 521 [51.5%] women) received two doses of vaccination with CoronaVac. The unvaccinated group consisted of 211 (17.3%) (mean [SD] age, 30.3 [6.9] years; 146 [69.2%] women) healthcare workers who refused vaccination throughout the study period.

Among 1012 fully vaccinated healthcare workers enrolled in the COVID-19 follow-up program, 35 (3.5%) SARS-CoV-2 infections were documented within six months. In this cohort (age range, 21-56; mean [SD] age, 34.8 [10.4] years; 22 [62.9%] women) COVID-19 cases occurred more frequently in females (62.9% vs 37.1%). Staff members, such as nursing staff and administration or maintenance workers were more frequently infected compared with academic staff (82.9% vs 17.1%). Demographic properties of the participants in both study groups were given in Table 1.

Twenty-seven (77.1%) of COVID-19 positive participants were diagnosed in the first 3-month period, and 8 (22.9%) in the second 3-month period. Though 34 (97.1%) of 35 healthcare workers diagnosed with COVID-19 had no previous history of COVID-19, one (2.9%) nurse working at the emergency unit had reinfection. She was asymptomatic when she was diagnosed for the second time.

During the 6-month follow-up of 211 unvaccinated participants, 16 (7.6%) (age range, 22-51; mean [SD] age, 30.3 [6.9] years; 9 [56.3%] men) became infected with SARS-CoV-2 confirmed by PCR. As expected, COVID-19 cases were more frequently seen in unvaccinated group compared to vaccinated group (7.6% vs 3.3%, respectively; P=0.003).

Eight (22.9%) of the vaccinated healthcare workers with COVID-19 were asymptomatic. They had to perform PCR test because they were in close contact with people who had COVID-19, as per the contact/case follow-up guide rules. Out of 35 vaccinated healthcare workers who were SARS-CoV-2 PCR positive 27 (77.1%) had at least one symptom at the time of diagnosis. Most common symptoms were flu-like symptoms such as runny nose, joint pain, fatigue, and headache. Out of 35 healthcare workers with COVID-19, 6 (17.1%) had coexisting illnesses; diabetes mellitus (n=4 [11.4%]), hypertension (n=3 [8.6%]), hyperlipidemia and sleep apnea (n=1 [2.9%] each). Four (11.4%) of them were followed up in hospital due to their existing diseases, one of who (2.9%) developed COVID-19 pneumonia and was discharged with recovery within two weeks.

All unvaccinated participants who became SARS-CoV-2 PCR positive

during the study period admitted with several symptoms to the hospital prior to their diagnosis. The most common symptoms were fever, malaise, cough, and joint pain. Four (25%) of 16 were hospitalized with the diagnosis of pneumonia due to COVID-19. One (6.3%) of those with pneumonia, a 46-year-old male radiology technician, died due to respiratory failure. Although all unvaccinated healthcare workers experienced symptomatic COVID-19, the vaccinated group suffered less from symptoms (100% vs 77.1%, respectively; P=0.045).

The incidence rate of symptomatic SARS-CoV-2 infection was 1.8 vs 4.4 per 10000 person- days in the vaccinated and unvaccinated cohorts, respectively, corresponding with an unadjusted IRR of 0.41 (95% CI, 0.23-0.74). Unvaccinated healthcare workers were 2.4 times more at risk of contracting COVID-19 than those of vaccinated. CoronaVac was 64.5% and 88.4% effective in preventing symptomatic and severe disease, respectively, and had an efficacy of 100% in preventing death among healthcare workers.

Anti-spike antibody evaluation of vaccinated healthcare workers (n=1012) showed that 99.6% had antibody results greater than 50.0 AU/mL (mean level, 1022.4 AU/mL) three weeks after the second dose of CoronaVac. All vaccinated participants with COVID-19 (n=35) had positive antibody levels before infection, and their mean antibody titer was higher than the mean antibody titer of all healthcare workers (1022.4 vs 1406.8 AU/mL) (Figure 1).

The humoral immune response before and after SARS-CoV-2 infection was analyzed in 23 of 35 vaccine breakthrough cases. The antibody results revealed that the median value of anti-spike antibodies (919.2; 351.1-1939.2 AU/mL) detected after two doses of vaccination in this group was extremely lower than the median value of antibodies (13743; 983.9- 32148.2 AU/mL) detected after the diagnosis of COVID-19 (Figure 2).

Table 1. Demographic properties of healthcare workers with COVID-19

Properties	**n (%)**
Gender	
Female	22 (62.9%)
Male	13 (37.1%)
Age (yrs)	
18-34	18 (51.4%)
35-59	17 (48.6%)
Units	
Academic Staff	6 (17.1%)
Hospital Staff	29 (82.9%)
Consultant	4 (11.4%)
Doctor	1 (2.9%)
Physiotherapist	2 (5.7%)
Nurse	9 (25.7%)
Administrative Staff	4 (11.4%)
Medical Student	1 (2.95%)
Auxiliary Staff	8 (22.95%)

Figure 1. Anti-spike antibody levels of vaccinated healthcare workers before COVID-19.

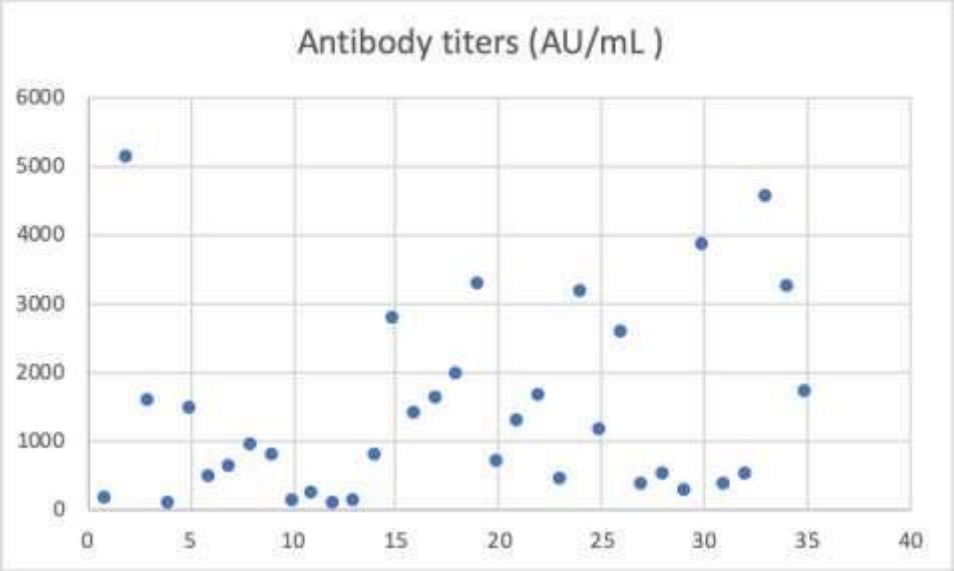
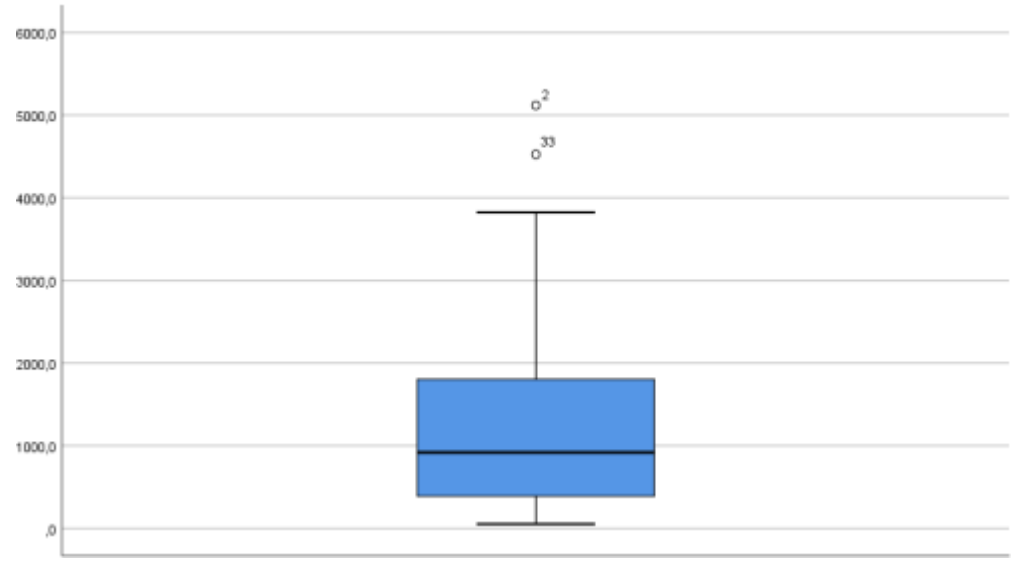
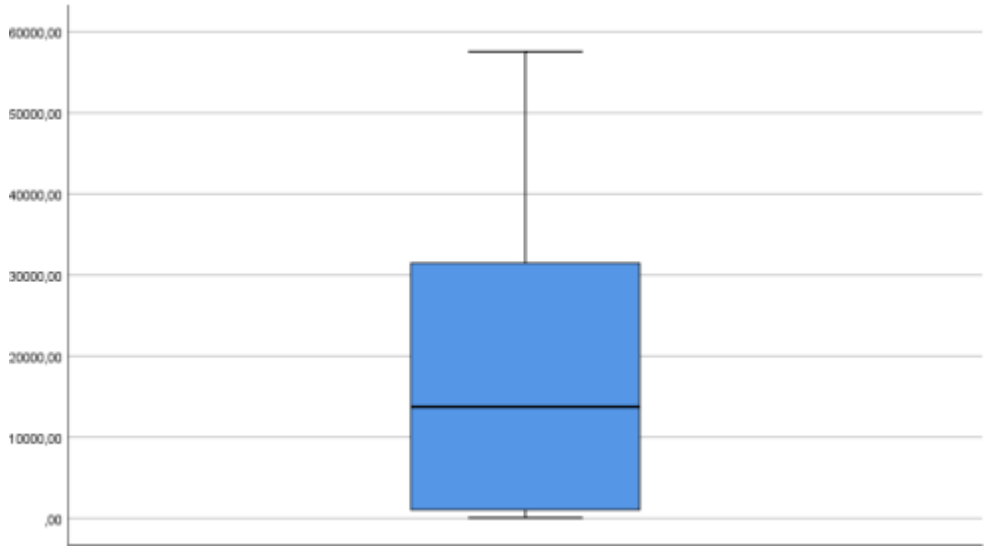


Figure 2. Immune response in healthcare workers (a) before and (b) after COVID-19.

(a)



(b)



Discussion

The effects of COVID-19 pandemic are seen more commonly in healthcare workers than in other occupational groups as they are at significant risk from prolonged direct exposure to the virus via patients with COVID-19. For this reason, priority was given to healthcare workers andolder adults when vaccination programs were initiated (6).

Although they have completed the full-dose vaccination program, the rate of COVID-19 in the first six months after CoronaVac was determined as 3.5% in healthcare workers of our hospital. About four-fifths (77%) of COVID-19 cases occurred within the first three months following vaccination, which made us think that the decrease in the number of cases in the second 3- month period may be due to the initiation of the vaccination program in the general population. It was seen that a widespread and effective vaccination program was one of the most effectivemethods of preventing the spread of the virus (7). Especially for RNA viruses, the higher the spread of the virus among humans, the higher the likelihood of mutations. While some mutations may make the virus more advantageous in terms of infectivity, in some mutations, the virus may cause more severe disease (8).

The Center for Disease Control and Prevention (CDC) has determined various classifications for variants (9). Concern variants (Variant of Concern, VOC) of SARS-CoV-2 are variants that have increased infectivity by reducing the efficacy of vaccines or drugs. The Alpha (B.1.1.7) variant, which was the first identified variant in the VOC group, was seen first in the United Kingdom in September 2020 and has spread rapidly globally (10). While the Alpha (B.1.1.7) variant was dominant at a rate of 85% in April in our country, the Delta (B.1.617.2) variant became more dominant as of July through August 2021 as in many other countries worldwide. The increase of COVID-19 cases in healthcare workers, especially in April 2021, made us thinkthat the Alpha (B.1.1.7) variant may have effect in the spread of the virus within the first 3-

month period of the follow-up.

With the emergence of highly infectious variants, there was a need to evaluate cases of reinfection to demonstrate the protective effect of vaccines against new mutations. The fact that

a fully vaccinated nurse working in emergency unit had COVID-19 confirmed by PCR after eight months for a second time, suggested that she was infected with a different variant of the virus. Among vaccinated healthcare workers, COVID-19 was mostly seen in nurses with a rate of 22.9%. In various studies, it has been reported that nurses have a higher incidence of disease compared to other healthcare professionals, and it is thought that this situation may be caused by a longer time of direct contact of nurses with the patients (11, 12).

In our study all (100%) unvaccinated healthcare workers with COVID-19 (n=16) admitted with several symptoms. Four (25%) of them developed COVID-19 pneumonia and one (6.3%) died due to respiratory failure caused by SARS-CoV-2. In vaccinated group however, symptomatic disease was seen in 77.1% of cases and only one (2.9%) out of 35 healthcare workers with COVID-19 developed pneumonia. This observation confirmed that CoronaVac prevented moderate and severe disease in vaccinated individuals (13).

Breakthrough infections after BNT162b2 messenger RNA vaccine have been reported in various studies. The incidence of COVID-19 was reported 2.6% (n=35) among 1497 vaccinated healthcare workers during 4-month period in Israel (14). Regev-Yochay et al. reported 1.8% COVID-19 in full-dose vaccinated healthcare workers, while this rate was 5.2% in unvaccinated staff. They reported that the incidence of symptomatic cases was significantly lower among fully vaccinated vs unvaccinated workers (15).

In Chile in a period of six months 45 (2%) breakthrough cases among 2263 volunteers were reported with SARS-CoV-2 infection over 14 days after the second dose of CoronaVac (16). In the present study, 3.5% SARS-CoV-2 infections were documented within the first six months following vaccination with CoronaVac. Both of the above studies were conducted at the same time period and in people vaccinated with the same vaccine which makes it easier to compare their results. We suggest that the volunteers being composed of healthcare workers may have increased the rate of contracting COVID-19 in our study.

Palacios et al. (17) found the efficacy of CoronaVac as 50.7% in volunteers between 18-59 ages. They reported that vaccination protected individuals 100% from very severe and moderately severe disease. Tanrıover et al. (18) reported 83.5% efficacy of CoronaVac in preventing symptomatic SARS-CoV-2 infection in a phase 3, placebo-controlled randomized clinical trial with 10214 participants between ages of 18-59. In a study conducted in Brazil the efficacy of CoronaVac was found as 77.6% in symptomatic cases and as 83.9% against hospitalization and death (19).

In our study, the incidence of COVID-19 among vaccinated vs. unvaccinated healthcare workers during a six-month follow up was 3.5 vs 7.6%, respectively, and the difference was statistically significant (P=0.003). The efficacy of

CoronaVac was 64.5% in preventing symptomatic COVID-19, 88.4% in preventing severe disease, and 100% in preventing death among healthcare workers. It was thought that the differences in vaccine efficacy between studies were due to the different number of volunteers and the diversity of COVID-19 case definitions.

All healthcare workers with COVID-19 had antibody titers above the threshold value (≥ 50.0 AU/mL) after the second dose of CoronaVac. This finding suggested that, at least in some cases of our study, the effect of vaccine-induced humoral immunity was limited and protected against symptomatic disease but not against infection. Immunity induced with BNT162b2 vaccine has been shown to be greatly protective against clinical disease but somewhat less protective against both infection and infectivity also (15). The degree of protection may depend more on the initial immune response than on the decay of antibody levels since memory cells are expected to respond to future exposures (14).

This study has some limitations; first, the cohort represented mostly young and healthy individuals, thus we could not guess protection from infection in vulnerable or older populations with coexisting diseases. Second, since we did not analyze the cycle threshold (Ct) values in COVID-19 cases, we could not make any comment regarding the viral load and infectivity of cases.

As a result of long-term exposure to SARS-CoV-2, mask and distance measures become ineffective from the protection of infection and more reliable results are obtained with vaccination. It is seen that the increase in the number of cases due to the increase of the variantsin the circulation affects the protection of the inactivated vaccine. In accordance with our findings, it was concluded that CoronaVac was highly effective in preventing severe disease and death in healthcare workers for a period of six months after two consecutive doses.

Competing interests statement

The authors declare that they have no conflicts of interest.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID- 19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-42.
2. World Health Organization. Regional Office for E. Health inequity and the effects of COVID-19: assessing, responding to and mitigating the socioeconomic impact on health to build a better future. Copenhagen: World Health Organization. Regional Office for Europe; 2020 2020. Contract No.: WHO/EURO:2020-1744-41495- 56594.
3. Callaway E. The race for coronavirus vaccines: a graphical guide. Nature. 2020;580(7805):576-7.
4. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. Science.2020;368(6494):948-50.
5. Azap-Kurt Ö AH, Erol Ç, Sarı N. Healthcare workers should be vaccinated with the highest effective vaccineavailable. Infect Dis Clin Microbiol 2021.3(2):107-8.
6. Noh EB, Nam HK, Lee H. Which Group Should be Vaccinated First?: A Systematic Review. InfectChemother. 2021;53(2):261-70.
7. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020;288:198114.
8. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2—What Do They Mean? JAMA.2021;325(6):529-31.
9. SARS-CoV-2 Variant Classifications and Definitions [Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html.
10. England P. Investigation of novel SARS-

CoV-2 variant: variant of concern 202012/01. PHE Technical Briefing. 2020.

11. Kramer V, Papazova I, Thoma A, Kunz M, Falkai P, Schneider-Axmann T, et al. Subjective burden and perspectives of German healthcare workers during the COVID-19 pandemic. European Archives of Psychiatry and Clinical Neuroscience. 2021;271(2):271-81.

12. Özdemir A, Demir Çuha M, Telli Dizman G, Alp A, Metan G, Şener B. [SARS-CoV-2 Seroprevalence Among Healthcare Workers: Retrospective Analysis of the Data From A University Hospital in Turkey]. Mikrobiyol Bul. 2021;55(2):223-32.

13. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. New England Journal of Medicine. 2021;385(10):875-84.

14. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. New England Journal of Medicine. 2021;385(16):1474-84.

15. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination: a prospective cohort study in Israel. The Lancet Regional Health-Europe. 2021;7:100150.

16. Duarte LF, Gálvez NMS, Iturriaga C, Melo-González F, Soto JA, Schultz BM, et al. Immune Profile and Clinical Outcome of Breakthrough Cases After Vaccination With an Inactivated SARS-CoV-2 Vaccine. Frontiers in Immunology. 2021;12(3884).

17. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JdP, Tilli Reis Pessoa Conde M, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. 2021.

18. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213-22.

19. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. Bmj. 2021;374:n2015.

Experimental and Applied Medical Science, 3,3: 430-436, 2022. DOI 10.46871/eams.2022.46

Leptin and Metabolic Effects

Feride Koca[1], Leyla Cimen[1]

[1]Gaziantep Islam Science and Technology University, Faculty of Medicine, Dept. of Medical Biochemistry, Gaziantep/ Turkey

Abstract

Leptin is a metabolic hormone secreted from adipose tissue, also called satiety hormone. This hormone plays an important role in the regulation of body weight and energy homeostasis. Studies have shown that deficiency or excess of this hormone causes many metabolic changes in our body (such as obesity, type 2 diabetes, cardiovascular diseases, cancer). In this review, the general properties of leptin and its effect on these metabolic diseases were examined.

***Keywords**:* leptin, metabolic diseases, obesity, diabetes mellitus, cardiovascular diseases

***Corresponding author:** Feride Koca. e-mail: feride.koca@gibtu.edu.tr. ORCID ID:0000-0002-5150-8029.

Introduction

Leptin is a protein-structured hormone consisting of 167 amino acids released from adipose tissue. It is encoded by the ob/ob gene in humans (1). This hormone has important effects on energy balance and food intake (2). It has been shown that leptin, which is synthesized mainly from adipose tissue in the body, is secreted to some extent by the placenta, gastric epithelium, skeletal muscle, pituitary and mammary gland (3).

Leptin, mainly synthesized and secreted by adipose tissue, shows function as a kind of antiobesity factor by regulating the balance between energy intake and energy expenditure by acting on its specific receptors in the hypothalamus. It has been demonstrated that leptin have many functions such as reproduction, hematopoiesis, regulation of gastrointestinal functions, angiogenesis, regulation of sympathetic nervous system activation, determination of bone density, thermogenesis and brain development (3).

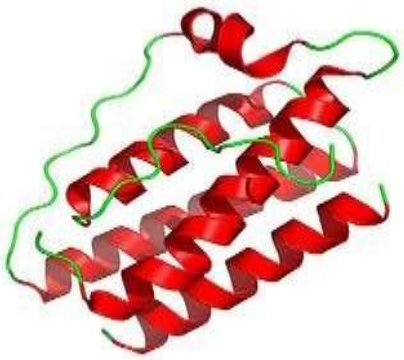
Structure of Leptin

Leptin has a quadruple helix structure and it structurally resembles members of the type 1 helical family (4).

All receptor types of leptin are encoded by the Lepr gene, but they exist in 6 forms, namely OBRa, OBRb, OBRc, OBRd, OBRe and OBRf, depending on cytoplasmic domains of different lengths as a result of alternative mRNAs used in translation and proteolytic processes. These receptors are members of the class 1 cytokine receptor family (5).

Leptin receptors are expressed in brain and peripheral tissues. Binding of leptin to its receptors leads to stimulation of receptors associated with the Janus kinase 2 pathway, resulting in phosphorylation of two tyrosine residues. Expression of leptin receptors such as ObRa and ObRb is seen in all tissues in mammals, but ObRb is only highly expressed in the hypothalamus (4).

The Tertiary Structure of Leptin. (6).



Secretion of Leptin

Leptin secretion is regulated by a several hormones, including insulin, glucocorticoids, and leptin itself. As lipid stores in the body increase, leptin secretion
in adipocytes increases accordingly. Therefore, changes in adipose tissue directly affect the change in leptin level in the blood (7). The secreted leptin is removed from the system via the kidneys and liver. The amount of circulating leptin is primarily energy stores in adipose tissue, but also varies according to hormonal balance, body fat ratio, skin thickness and gender (5).

Leptin is a besides secreted at low levels in other tissues such as bone marrow, ovary, placenta, stomach, and lymphoid tissue. Short isoforms of leptin, ObRa and ObRc, are thought to have effects on the transport of leptin across the blood-brain barrier. ObRb, the long isoform of leptin, is present everywhere in the central nervous system and plays a primary role in leptin signaling. The ObRb receptor is incredibly important in the hypothalamus as it regulates energy balance and neuroendocrine functions. In humans, the release of leptin into the circulation is pulsatile. Leptin concentrations follow a circadian rhythm and are affected by sleep patterns. It has been shown that the highest leptin levels are between midnight and early morning, and the lowest leptin levels are between morning and afternoon. (8).

The secretion of leptin hormone from the adipose tissue is determined by the level of the hormone in the circulation. This hormone primarily decreases food intake through its hypothalamic receptors and increases metabolic rate. Leptin is found in the circulation both free and bound to leptin-binding proteins. The free/total leptin ratio is independent of physiological states such as hunger and satiety. However, there is probably a dynamic balance between binding proteins and free leptin, which can be affected by metabolic events. It has been reported that most of the leptin is found in bound form in thin people and in free form in obese people (9).

Metabolic and Physiopathological Effects of Leptin

Leptin exerts its metabolic effects by interacting with receptors in the central nervous system and peripheral tissues (lung, kidney, liver, heart, endocrine part of the pancreas, adrenal glands, uterus, ovary, testis, hematopoietic cells, skeletal muscle, etc.). Leptin receptors, whose main area of action is the hypothalamus; it is located within the hypothalamic area, which is related with the control of appetite, reproduction and growth (10).

After the leptin gene was discovered, it was understood that leptin inhibits the synthesis and release of neuropeptide Y (NPY) in the arcuate nucleus (ARC). With this effect, it has been understood that leptin regulates appetite and metabolism (11). While leptin increases glucose uptake and expenditure in brown adipose tissue, it decreases glucose uptake by suppressing glucose transporters in white adipose tissue. It stimulates glycogen synthesis by reducing insulin resistance in liver tissues,

while muscle increases fatty acid oxidation by decreasing glycogen synthesis. Leptin increases fatty acid uptake and oxidation by inhibiting the activities of regulatory enzymes involved in fatty acid synthesis. In general, it increases the use of oxygen in the tissues and induces the use of fats as an energy source. In addition, it provides lipid balance in the body by reducing the intracellular lipid level in skeletal muscle, liver and pancreas (5).

Leptin and Obesity

Obesity is described as an excessive increase in body fat mass relative to fat-free mass. Obesity is a serious public health problem as it is associated with insulin resistance, diabetes, atherosclerosis, hypertension, chronic kidney disease, and increased cardiovascular morbidity and mortality (12).

The hormone leptin plays an substantial role in producing energy and regulating food intake. Deficiency of this hormone or formation of leptin resistance causes obesity in humans (13).

Many studies have found a strong positive relationship between serum leptin levels and body fat percentage. As the amount of adipose tissue increases, leptin levels in the body increase rapidly, and by binding to its receptor in the hypothalamus, it reduces appetite, but does not completely stop eating. Leptin stimulates lipolysis in adipose tissue and inhibits insulin release from beta cells in the pancreas (13).

Leptin levels decrease in situations that cause a decrease in fat mass, such as calorie restriction, hunger, and illness. As a result, the sympathetic nervous system response is reduced, the hypothalamus is stimulated, and signals that inhibit appetite are reduced. In obesity, leptin resistance occurs, which is characterized by the inability to detect the amount of leptin in the body by the brain, and the lack of feeling of satiety and the inability to suppress the feeling of hunger. Although circulating leptin is high, the brain cannot receive satiety signals and this causes hyperphagia (14).

With the decrease in fat stores, leptin decreases, increasing appetite and food intake. In other words, with a decrease in leptin level, food intake increases while energy expenditure decreases. The increase in fat stores reduces appetite by increasing leptin, and in this way, food intake is reduced (10).

Leptin secretion increases in obesity and leptin resistance develops due to inflammation. Insulin and leptin signaling pathways are the main pathways that regulate the nutrient and energy balance in the body. Leptin exerts insulin-like effects on glucose metabolism. Basically, it provides body weight control by showing an appetite suppressant effect. Some studies have shown that acute injection of leptin into mice improves glucose metabolism and insulin sensitivity (15).

In the study conducted by Yigitbası T et al, it was determined that the leptin level in overweight and obese patients was higher than in normal individuals. In the same study, the relationship between leptin level and insulin resistance seen in obesity was also investigated. The leptin levels in

the insulin resistance positive obese group and the insulin resistance negative obese group were compared and no statistically significant difference was observed between them. As a result of this study, it has been demonstrated that leptin is associated with body mass index (16).

Leptin and Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder that usually occurs as a result of a combination of hereditary and environmental factors and results in an excessively high blood glucose level (hyperglycemia). The regulation of blood sugar in the body is achieved as a result of the complex interaction of many chemicals and hormones. The most important hormone that plays a role in the regulation of sugar metabolism is insulin, which is secreted from the beta (β) cells of the pancreas. DM may occur as a result of either a deficiency in insulin secretion or a defect in the action of insulin. In summary, DM is a complex disease characterized by defect in carbohydrate, fat and protein metabolism, various microvascular and macrovascular complications occurring simultaneously, and an increase in glucose changes in the blood. All subtypes of DM result from inadequate insulin supplementation or from a lack of tissue response due to the insulin being unable to exert its effect. Diabetes is generally divided into two types as type I diabetes and type II diabetes. Type I diabetes results from the destruction of β-cells involved in insulin production in pancreatic is lets by autoimmune pathway. Type II diabetes, on the other hand, is a progressive disease that results from the combination of insulin resistance and β-cell system dysfunction (17).

Studies in recent years have shown that leptin has effects such as regulating blood glucose levels and increasing insulin sensitivity (9). In a study conducted with type 2 DM patients, insulin was given to the patient and it was revealed that the leptin level increased after a long time, although not acutely. It is thought that the reason for this is the increase in the synthesis of leptin, a stimulating factor in adipocytes, by feeding the adipose tissue with insulin taken from the outside. In another study, it was demonstrated that leptin levels in type 2 DM patients with the same body mass index and non-diabetic individuals were not statistically different (5).

Leptin and Coronary Heart Diseases

Coronary artery disease (CAD) is the main cause of death in our country as well as in industrial western societies. Obesity is one of the most important risk factors for hypertension and atherosclerosis. It is stated that adipokines secreted from adipose tissue are very important for the development of obesity-related diseases such as CAD, diabetes and cancer (18).

In a prospective study examining the relationship between leptin and CAD, it was suggested that leptin may be an independent risk factor for CAD. These data suggest that leptin may affect the vascular structure. In vitro and in vivo studies have shown that leptin has an angiogenic effect and contributes to arterial thrombosis

through platelet leptin receptors (18). Studies have reported that individuals with coronary heart disease have higher leptin levels than controls. However, contrary to these studies, there are also studies supporting that there is no relationship between leptin and CAD (19).

Leptin and Cancer

Cancer is a serious health problem that ranks second among the causes of death in the world, has a high mortality and morbidity rate, causes anxiety about the future and uncertainty, and threatens life (20).

Studies have shown that obesity increases the risk of cancer formation. Leptin is thought to regulate the expression of genes associated with cancer progression. This suggests that it directly supports the growth of adipocytes in the tumor microenvironment. Leptin receptors are highly abundant in many tumors compared to

normal tissues, such as leptin-responsive mammary carcinoma and gastrointestinal malignancies. With this feature, leptin signal creates synergy with many different oncogenes, cytokines and growth factors that affect the same signaling pathways (21). Leptin may affect the risk of breast cancer by increasing estrogen synthesis or decreasing follicular estradiol synthesis. Leptin shows its effect by increasing cell survival and proliferation together with estrogen receptor-α. This explains the positive relationship between estrogen and leptin systems in human breast cancer development. It has been reported that circulating adiponectin levels are lower in overweight and obese adults, while leptin levels are higher than in thin individuals. Low adiponectin and increased leptin levels were related with an increase in breast cancer. Studies have shown that an increase in the ratio of adiponectin to leptin reduces the proliferation of breast cancer cells; no such effect was observed when the ratio of leptin to adiponectin was increased. Therefore, it is thought that the ratio between leptin and adiponectin is more important in the regulation of breast cancer development rather than the effect of a single adipokine (22).

Adipose tissue dysfunction caused by obesity plays an important role in carcinogenesis by affecting the production of various adipokines. Among these adipokines, leptin has been shown to play an important role in the progression and recurrence of cancer in epidemiological, pathophysiological and mechanistic studies (22).

Conclusion

Leptin is closely related to many metabolic diseases and it is an important adipokine that affects the entire metabolism. Leptin is not only a hormone that controls body weight and energy homeostasis, but also plays an important role in blood glucose regulation, inflammation, and cancer formation. It is important to elucidate leptin signal molecules and their mechanisms of action, as well as to investigate the diseases they cause. More studies are needed to understand the molecular and physiological mechanisms of the effect of leptin on these diseases.

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

Acknowledgement: No financial support was received from any institution for the research.

References

1. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372:425-32.

2. Pico C, Palou M. Leptin and metabolic programming. Nutrients. 2022; 14 ; 114

3. Aslan K, Serdar Z, Tokullugil A. Multifonksiyonel hormon: Leptin. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2004; 30 (2); 113-11.

4. Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. Cytokine. 2019;121:154735.

5. Keleş V, Büyükgüzel K, Büyükgüzel E. Leptin ve metabolik düzenlemedeki rolü. Türkiye Diyabet ve Obezite Dergisi. 2018; 1 : 17-22.

6. Uzun T, Bayraktar B. Leptin hormonunun bazı fizyolojik sistemler üzerindeki etkisinin incelenmesi. Bayburt Üniversitesi Fen Bilimleri Dergisi. 2019; 2(1) ; 104-109.

7. Zhou Y, Liangyou R. Leptin signaling and leptin resistance. Front Med. 2013 ; 7(2) : 207-222.

8. Mantzoros CS, Magkos F, Brinkoetter M, et al. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab. 2011; 301(4):E567–E584.

9. Gültürk S, Demirkaşık A. Leptin ve diyabet. Cumhuriyet Üniversitesi Tıp Fakültesi Dergisi. 2007; 29: 35-40.

10. Comba A, Mert H, Comba B. Leptin ve metabolik etkileri. Yüzüncü Yıl Üniversitesi Veteriner Fakültesi Dergisi. 2014;25(3) : 87-91.

11. Obradovic M, Milovanovic ES, Soskic S, et al. Leptin and obesity: Role and clinical implication. Frontiers in Endocrinology. 2021; 12(5).

12. Motor S, Keskin MC, Dokuyucu R. Obezite ve adipokinler. Mustafa Kemal Üniversitesi Tıp Fakültesi Dergisi. 2014;18;5: 34-45.

13. Özen Ş , Özen G. Leptin hormonu: Obezite ve egzersiz ile İlişkisi. e-Journal of New World Siences Acedemy Sport Sciences. 2011; 6 ; 2 :114-127.

14. Şahin T, Tozcu D. Leptin mikrobiyota ve obezite ilişkisi. Türkiye Diyabet ve Obezite Dergisi. 2022;1:77-84.

15. Göktaş Z, Besler HT. Obezite, insülin direnci ve bazı adipokinler. Beslenme ve Diyetetik Dergsi. 2015; 43(3); 251-257

16. Yiğitbaşı T. Obez hastalarda büyüme hormonu, leptin, amilin, glukagon benzeri peptid-1 seviyeleri ile insülin direnci arasındaki ilişki. Türk Biyokimya Dergisi. 2010;35(3):177- 182.

17. Taşkın E, Güven C, Kaya ST, et al. Diyabette leptin hormonunun olası etkileri. Düzce Üniversitesi Bilim ve Teknoloji Dergisi. 2019 (7) ; 1969-1975.

18. Güneş Y, Eröz E, Özarda Y, et al. Sağlıklı bireylerde ve kardiyovasküler hastalığı olan olgularda adiponektin, leptin, rezistin düzeylerinin değerlendirilmesi ; Bursa çalışması. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2011;37 (2) ; 77-81.

19. Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. Acta Pharmacologica Sinica. 2018; 39; 1176-1188.

20. Akeren Z, Hintistan S. Kanser hastalarının semptom yönetiminde aroma terapi kullanımı. Dergi Park. 2021;4(3):136-154.

21. Candia P, Prattichizzo F, Garavelli S, et al. The pleiotropic roles of leptin in metabolism, immunity, and cancer. Journal of Experimental Medicine. 2021; 218; (5).

22. Urhan M, Akbulut G. Obezite ve kanser ilişkisi: leptin kanserojen bir adipokin midir? İzmir Kâtip Çelebi Üniversitesi Sağlık Bilimleri Fakültesi Dergisi. 2017; 2(3): 35-43.