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

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Aim

Experimental and Applied Medical Science 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.

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.

Scope

Experimental and Applied Medical Science is an open-access, internationally double-blind peer reviewed academic medical journal which is published in English four times a year, under the auspices of Medical Faculty of Gaziantep Islam Science and Technology University. The journal receives manuscripts for consideration to be publishing in the form of research articles, reviews, letter to editor, brief notification, 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.

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 çalışmaları, klinik, farmakolojik, epidemiyolojik, deontolojik çalışmalar ile beraber halk sağlığının geliştirilmesi amacı taşıyan ve sağlık hizmetleri veya sağlık sigortaları konularında araştırma makaleleri, derlemeler, vaka sunumları, 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.

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Manuscripts are only considered for publication provided that they are original, not under consideration simultaneously by another journal, or 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 any manuscript is considered to deserve publishing, it may be subject to editorial revisions 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 below.

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

Manuscripts presenting data obtained from 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*

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Makaleler, orijinal/özgün olmaları, eş zamanlı olarak başka bir dergi tarafından incelenmemeleri veya daha önce yayınlanmamış olmaları koşuluyla yayına kabul edilir. 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.

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Editör Kurulu, "insan" ile yapılan tüm raporlanan veya sunulan çalışmaların bu ilkelere uygun olması gerektiğini beyan eder. 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* bölümünde, internet adresi aşağıda

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

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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 başvuru sistemi üzerinden gönderilmelidir. Dergi ile ilgili kullanım kılavuzları, teknik bilgiler ve gerekli formlar derginin internet sayfasında yer almaktadır.

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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 hazırlamak yazarların sorumluluğundadır.

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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 editorial correspondence must be submitted online to the editorial office, 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 have been added in time, all kinds of publication rights of the articles accepted

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, kaynaklar ve varsa biyoistatistiksel kısımlar açık, anlaşılır ve tatmin edici olmalıdır.

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Manuscripts should be prepared electronically using an appropriate “office word” compatible text-processing package, 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. Pages should 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 için 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) Teşekkür, 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 specific word lengths for any manuscript. The general principle is that a manuscript can be as long as necessary to communicate clearly and most effectively the scientific message, but should be as short as possible to achieve a complete presentation of the information without undue repetition or redundancy.

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. All dimensions and measurements must be

3. Gereç ve Yöntemler
4. Sonuçlar
5. Tartışma
6. Bağlam
7. Çıkar çatışması
8. Teşekkür, 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 uzun olabileceği, ancak gereksiz tekrar veya fazlalık olmadan bilgilerin eksiksiz bir sunumunu 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

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 without 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, et al. 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 asit fenetil ester (KAFE) ve miyokardiyal

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.

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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.

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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.

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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.

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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.
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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.

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Bilimsel araştırmalarınızı desteklemek ve geliştirmek için elektronik ek materyaller kabul edilmektedir. Ek dosyalar, yazara, destekleyici uygulamaları, filmleri, animasyon dizilerini, yüksek çözünürlüklü

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görüntüleri, arka plan veri kümelerini, ses kayıtlarını ve daha fazlasını yayınlamak için ek olanaklar sunmaktadır.

Başvuru sırasında çıkar çatışmasının ve mali 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

The Chancellor's Message

Dear Students and Academicians,

Islam has placed a huge emphasis on medicine, since the beginning. According to the Islamic opinion, obeying certain medicinal recommendations is indispensable for a Muslim for both his and all society's good. Recently, the world has lived through unfortunate memories because of the pandemic. That is the neither the first nor the last threat for humanity. Hadiths narrated by Islamic scholars were even able to shed light on how to be at war with contagious diseases, epidemics or pandemics, for many centuries. Our beloved prophet, beloved servant of Allah (C.C), Hz. Muhammed said that "If you hear of a plague somewhere,do not enter into there. If the plague occurs in your place, do not leave there", narrated by famous Islamic scholar Buhârî. This most fundamental principle for the fight against epidemics still remains valid today.

All advices regarding the medicine internalised from verses of the Quran, hadiths and the life of Hz. Muhammed are actually a set of principles, named as "Tıbb-ı Nebevî". Tıbb-ı Nebevî means medicinal principles and remarks of our prophet, Hz. Muhammed. It acts as a guideline for Muslims in certain major medical entities, such as general medicine, preventivemedicine and treatment approaches. Hadith mentioned above obviously points out certain principles of preventive medicine. Besides, there are others, for instance, in a verse of the Quran, Allah (C.C) Almighty orders that mothers should breastfeed their babies for two years. Today, scientists announce a number of research studies revealing the benefits of breast milk and they suggest that a baby should be breastfed for two years provided that thebaby should take only breast milk, not any other food supplement, during the first six months of the life.

We can find out lots of medicinal principles mentioned in the Quran or hadiths narrated by Islamic scholars. Also, Islamic world has managed to train honoured medical scientists during ages. One of famous medical scholars of his period was Ibn Sînâ who is well known with its original perspective into the medicine and adapting to orders of the Quran and medicinal principles of "Tıbb-ı Nebevî", really worth mentioning here. He wrote more 100 books in the fields of medicine and philosophy and these were utilised in Europe as reference books until 18th century.

I believe in that Gaziantep Islam, Science and Technology University Medical Faculty will be inspired by this great medicinal and cultural richness and will take its place in the modern medical world. I wish great success to the Medical Faculty Journal "Experimental and Applied Medical Science".

Wish you all the best

Prof. Dr. Mehmet Nihat Hatipoğlu
Chancellor of Gaziantep Islam Science and Technology University

Chief Editor's Message

Dear Readership,

While struggles continue at full speed to start education and training in our Faculty of Medicine which was brought to our country within the newly formed Gaziantep Islamic Science and Technology University, it has been one year since the "Experimental and AppliedMedical Science" sprouted, which is the academic publication of our Faculty of Medicine andin which we wholeheartedly believe will make a significant contribution to our academic community. We are very happy to deliver the fifth issue of our academic magazine to our readership in print, as well as in electronic form.

Nowadays, academic studies are accelerating, multiplying and diversifying. The need for channels where scientific studies, opinions and ideas can be freely expressed and easily shared with experts, researchers or postgraduate students who are still in the learning phaseis increasing day by day. "Experimental and Applied Medical Science" has adopted it as a principle from the first day to bring together original and up-to-date studies, stimulating scientific views and ideas from every field of medicine that will potentially increase the quality of life with its readers both from home and abroad. With this fifth issue of our journal, we will continue to publish in English 4 (four) times a year, more than thirty manuscripts , in different types, research articles, case reports, reviews, etc. will have already been published and met with our readers. Recently, researchers have begun to understand the importance of having their studies published in international double-blind peer-reviewed journals. Since the first day of its publication, "Experimental and Applied Medical Science" has subjected the manuscripts which have been received, to an international double-blind peer reviewed evaluation process. For this reason, we aim not only to evaluate the manuscripts submitted with an aspect in which we decide whether the manuscript deserves to be publishing or not, but also to help researchers improve their educational or academic lives by providing on-the-spot feedback.

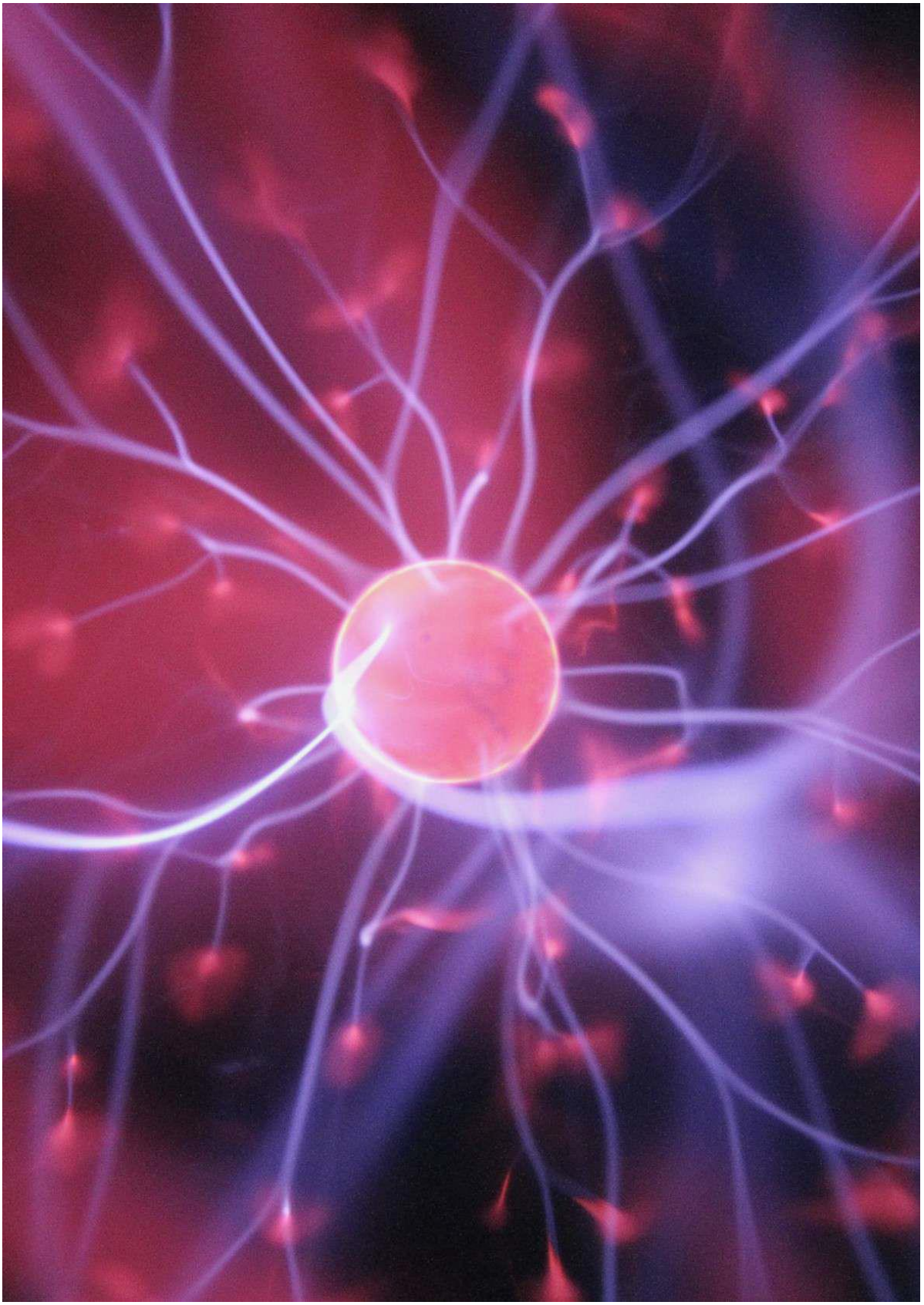
We are also happy that "Experimental and Applied Medical Science" which is only at the beginning of the road, has come a long way in a short time. In its 1 (one) year academic publication life, it has already started to be followed in nearly ten national or international indexes.

I would like to express my gratitude to our editorial and publishing boards, the esteemed academics who chose "Experimental and Applied Medical Science" for their manuscripts to have been submitted, all our readers, and our Rectorate for their unwavering support. I wish "Experimental and Applied Medical Science" the best success in its publication life.

Best Regards…

Chief Editor
Hamit Yıldız, Assoc. Prof.
Gaziantep University, Faculty of Medicine, Department of Internal Medicine

Contents/İçindekiler



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Role of Systemic Inflammatory Markers in Pulmonary Embolism Severity and Mortality

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Abstract

Pulmonary embolism is a thromboembolic disease with high morbidity and mortality rates. Ratio of Monocyte-to-HDL cholesterol (MHR) could be present the inflammatory status of patients. The aim of this study was to research the association of MHR, which is a new marker in predicting the prognosis of patients with pulmonary embolism. Patients who were followed up in our hospital with the diagnosis of pulmonary embolism between October 2016 and June 2020 were included in the study. Patients' demographic data such as age and gender, vital findings, comorbid diseases, lipid profiles, renal function tests, hemogram outcomes at admission, electrolyte values and cardiac markers were recorded and analyzed. Patients' pulmonary embolism (PE) clinical classes were determined. The correlations between monocyte/HDL-cholesterol ratio and PE severity were analyzed. A total of 160 patients followed up in our hospital due to PE were included in the study. Of all patients 38.2% (n=60) were diagnosed with massive and 61.8% (n=100) non-massive PE. There were statistically differences between Non-massive and massive PE in terms of Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, Monocytes/ HDL ratio, sPAB and Survive status (p=0.035, p=0.004, p=0.046, p=0.000, p=0.008, p=0.031, p=0.001, p=0.000, p=0.000, and p=0.000, respectively). There was a positive correlation between PE severity and Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, MHR, sPAB and Survive status. Of all patients included in this study, 43 patients (71.2%) died in the massive group and 16 patients (15.5%) were died in the non-massive group. However, MHR was higher in patients who died (0.092±0.17) compare to survivor (0.015±0.00) (p=0.000). Monocyte-to-HDL-cholesterol ratio, which is an inexpensive marker easily available in all centers, can be used in acute pulmonary embolism for PE severity status and mortality status.

Key words: *Pulmonary embolism, Prognosis, Monocyte–HDL, Mortality.*

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Introduction

Pulmonary embolism (PE) is an acute thromboembolic disease with high rates of morbidity and mortality (1, 2). According to a study from the USA, 42 million deaths occurred within 20 years with 600.000 (1.5%) of these being due to PE (3). As in many emergencies, an early and correct diagnosis is vital in PE. However, since clinical features of PE are not specific, it is not easy to establish the diagnosis of PE. The rate of mortality decreases below 10% if the diagnosis is established correctly and in an early stage in PE (2, 4).

Venous thromboembolism resulting in PE causes a series of inflammatory reactions in the pulmonary artery wall with increased cell flow and release of cytokines and chemokines (5). Therefore, studies are investigating the effectiveness of various inflammatory markers in determining vascular inflammation. Studies have reported that systemic inflammation from PE will be determined by the neutrophil to lymphocyte ratio (NLR) in the near future and NLR will be used to predict mortality in PE (6, 7). One of the recently proposed parameters for the determination of systemic inflammation is the monocyte-HDL-cholesterol ratio (MHO). Monocytes, as a source of various cytokines and molecules, interact with circulating platelets and endothelial cells, resulting in the accumulation of inflammatory and pro-thrombotic pathways (8). HDL-C, on the other hand, abolishes these proinflammatory and pro-oxidant effects of monocytes by inhibiting the migration of macrophages. Therefore, MHO can indicate a patient's inflammatory state. It has been stated in previous studies that MHO may be a new cardiovascular prognostic marker (9, 10). However, the number of studies investigating the efficacy of MHO in predicting the prognosis and severity of PE is limited.

The aim of this study is to investigate the relationship of MHO, a new marker, in predicting the prognosis of patients with pulmonary embolism.

Materials and methods

This study was designed as a retrospective cohort study. Before the start of the study, the study protocol was approved by the local ethics committee of our hospital (Approval no: 2020.09.1.10.127). Patients followed-up and treated with the diagnosis of PE in our hospital between January 2016 and December 2020 were included in the study. Patient files were screened via the hospital registry system and patient's data were retrospectively screened and recorded. Patients' demographic data such as age and gender, vital findings, hemogram outcomes at admission (hemoglobin, neutrophil, platelets, lymphocytes, monocytes), lipid profiles (triglycerides, HDL, LDL), liver function tests (ALT, AST, albumin), renal function tests (urea, creatinine), electrolyte values (magnesium, calcium, phosphorus) and cardiac markers (troponin I) were recorded and analyzed. In addition, echocardiography (ECG) findings, blood gas values and patient outcomes at follow-up (follow-up in ward, referral to intensive care, exitus) were also recorded. Patients' pulmonary embolism (PE) clinical classes were determined and PESI test values were calculated. PE severity was determined in accordance with the Turkish Thoracic Society Thromboembolism Guidelines and classified based on ECG findings as massive (high risk), sub-massive (moderate risk) and non-massive (low risk) (13). Accordingly; patients with hypotension refractory to treatment were considered as

massive PE, those with normal systemic blood pressure, but right ventricular dysfunction on echocardiography as submassive PE, and patients with normal systemic blood pressure and right ventricular function as non-massive PE.

The data obtained in this study were analyzed using the statistical program SPSS v.25 (SPSS, Chicago, USA). Descriptive statistics such as frequency distribution, mean and standard deviation were used to evaluate the data. The normality control of the data was done with the Shapiro Wilk test. The difference between the means of two independent groups was compared with Student's t test, and the differences between more than two groups were compared with analysis of variance and parametric test. Mann-Whitney U and Kruskal-Wallis tests, which are non-parametric alternatives of these tests, were used when parametric test assumptions were not met. ROC analysis was used to determine the cut-off point, the area under the curve (AUC), the sensitivity (sensitivity) and the specificity (specificity) of the data. Categorical data were analyzed with Chi-square or Fisher's Exact test. $p < 0.05$ values were considered statistically significant at the 95% confidence interval.

Results

The comparison of patients' socio-demographic, clinical and laboratory parameters was shown in Table 1. Of all patients 38.2% (n=60) were diagnosed with massive and 61.8% (n=100) non-massive PE. There were statistically differences between Non-massive and massive PE in terms of Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, Monocytes/ HDL ratio, sPAB and Survive status (p=0.035, p=0.004, p=0.046, p=0.000, p=0.008, p=0.031, p=0.001, p=0.000, p=0.000, and p=0.000, respectively).

The correlation analysis between MHR and other variables was shown in Table 2.

There was a positive correlation between PE severity and chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, MHR, sPAB and survival status.

As a result According to ROC analysis for massive PE, MHR was significant prognostic factor (AUC: 0.751, p=0.001, min-max: 0.660-0.842) (Figure 1).

Of all patients included in this study, 43 patients (71.2%) died in the massive group and 16 patients (15.5%) were died in the non-massive group. However, MHR was higher in patients who died (0.092±0.17) compare to survivor (0.015±0.00) (p=0.000) (Figure 2).

Table 1: Comparison of patients' socio-demographic, clinical and laboratory parameters.

Parameters	Non-massive (N = 100, 61,8 %) Mean ± SS (min-max), n (%)	Massive (N = 60, 38,2 %) Mean ± SS (min-max), n (%)	P
Age (year)	67.0 (21-91)	71.50 (31-88)	0.106
Gender			0.495
Male	34 (% 34.5)	24 (% 40.4)	
Female	66 (% 65.5)	36 (% 59.6)	
Coronary artery disease	21 (% 21.4)	14 (% 23.1)	0.823
Heart failure	5 (% 4.8)	4 (% 5.8)	0.798
Cancer	19 (% 19.0)	15 (% 25.0)	0.414
Hypertension	64 (% 64.3)	45 (% 75.0)	0.194
Hyperlipidemia	7 (% 7.1)	5 (% 7.7)	0.906
Diabetes mellitus	37 (% 36.9)	27 (% 44.2)	0.400
Cerebrovascular disease	12 (% 11.9)	10 (% 17.3)	0.381
Atrial fibrillation	7 (% 7.1)	7 (% 11.5)	0.384
Chronic renal failure	15 (% 15.5)	18 (% 30.8)	0.035
COPD	15 (% 15.5)	12 (% 19.2)	0.574
Deep vein thrombosis	58 (% 58.3)	31 (% 51.9)	0.468
Hemoglobin (g/dL)	11.83±1.7 (7.0-15.4)	11.95±2.1 (8.1-16.0)	0.715
troponin (pg/mL)	100.5±194.3 (0.0-920.0)	224.3±391.6 (4.3-1933.0)	0.004*
D-dimer (pg/dL)	5.42±3.5 (0.1-14.2)	7.11±3.8 (0.1-15.8)	0.046
HDL (mg/dL)	43.3±12.1 (9.0-82.0)	31.5±10.1 (12.0-64.0)	0.001*
LDL (mg/dL)	127.2±41.2 (25.0-253.0)	124.1±44.4 (37.0-252.0)	0.698
Total cholesterol (mg/dL)	198.5±52.9 (74.0-337.0)	191.6±55.2 (71.2-338.0)	0.492
Triglycerides (mg/dL)	157.1±79.4 (48.0-565.0)	155.6±75.0 (59.0-483.0)	0.922
CRP (mg/dL)	64.53±70.7 (1.7-401.0)	74.92±84.8 (4.1-364.8)	0.443
Creatinine (mg/dL)	1.00±0.8 (0.3-7.4)	1.24±1.0 (0.5-7.0)	0.008*
Albumin (g/dL)	3.50±0.7 (1.7-4.8)	3.41±0.6 (2.1-4.8)	0.461
White Blood Cell (103/µL)	10.26±4.7 (1.0-29.3)	12.48±1.0 (4.8-45.7)	0.031
Neutrophils (109/L)	6.87±4.8 (0.1-27.0)	7.85±5.8 (0.1-32.3)	0.294
Lymphocytes (109/L)	3.98±6.1 (0.3-42.0)	3.54±4.8 (0.2-25.0)	0.667
Platelets (109/L)	244.47±89.7 (56.0-562.0)	243.64±112.6 (4.7-603.0)	0.962
Monocytes (109/L)	0.73±0.31 (0.0-1.9)	2.06±3.9 (0.3-27.0)	0.001*
Platelet / lymphocyte ratio	149.44±130.6 (5.6±661.4)	157.77±179.3 (1.6-1162.5)	0.757
Neutrophil / lymphocyte ratio	4.79±5.5 (0.0-28.6)	6.50±9.7 (0.0-54.5)	0.200
Monocyte / HDL ratio (MHR)	0.019±0.01 (0.00-0.06)	0.083±0.17 (0.00-1.22)	0.001*
sPAB (mmHg)	34.47±7.6 (20-55)	54.45±11.8 (30-90)	0.001*
Survival status			0.001*
Yes	84 (% 84.0)	17 (% 28.8)	
No	16 (% 16.0)	43 (% 71.2)	

*: Mann–Whitney U was applied. COPD: Chronic obstructive pulmonary disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, sPAB: Systolic pulmonary artery pressure.

Table 2: Correlation analysis between MHR and other variables.

	Correlation coefficient (r)	**P**
Massive PE	0.423**	0.001
Death rate	0.561**	0.001
Chronic renal failure	0.225**	0.008
Troponin	0.136	0.138
D-dimer	0.160	0.143
HDL	-0.753**	0.001
LDL	-0.234**	0.010
Total cholesterol	-0.235**	0.010
Creatinine	0.130	0.132
White blood cell	0.407**	0.001
Neutrophils	0.275**	0.001
Monocytes	0.898**	0.001
CRP	0.309**	0.001
Albumin	-0.245**	0.004
Neutrophil / lymphocyte ratio	0.186**	0.032
sPAB (mmHg)	0.357**	0.001

HDL: High-density lipoprotein. sPAB: Systolic pulmonary artery pressure.

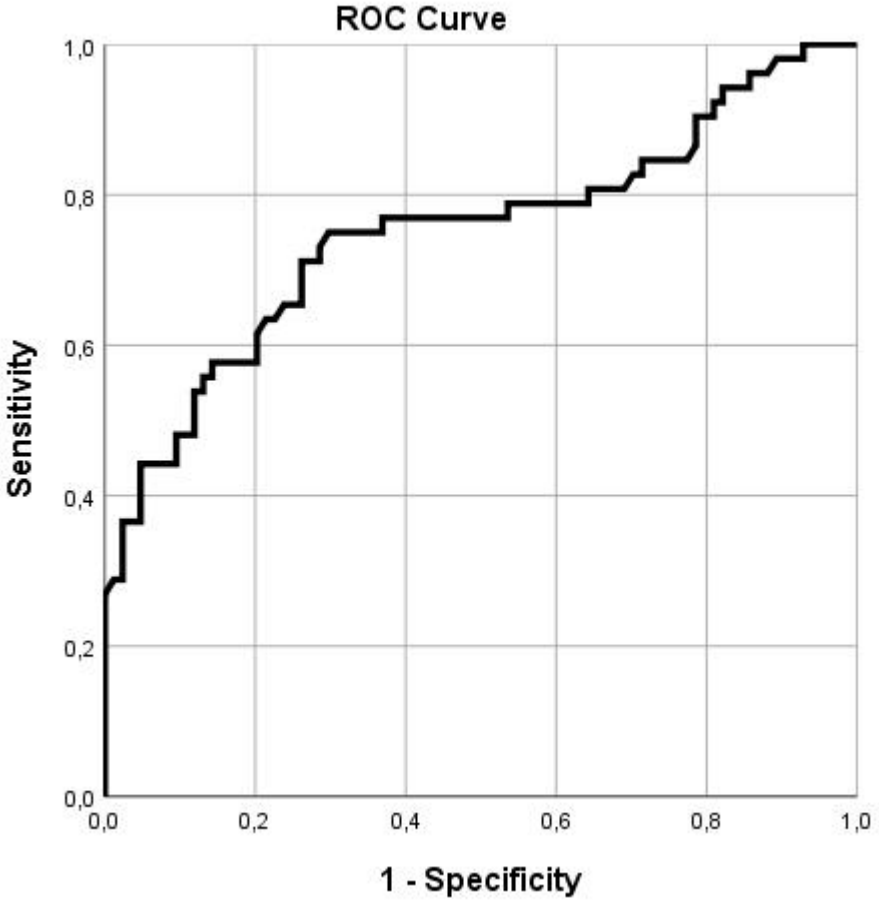

Figure 1: ROC analysis results in patients with massive pulmonary embolism. Diagonal segments are produced by ties.

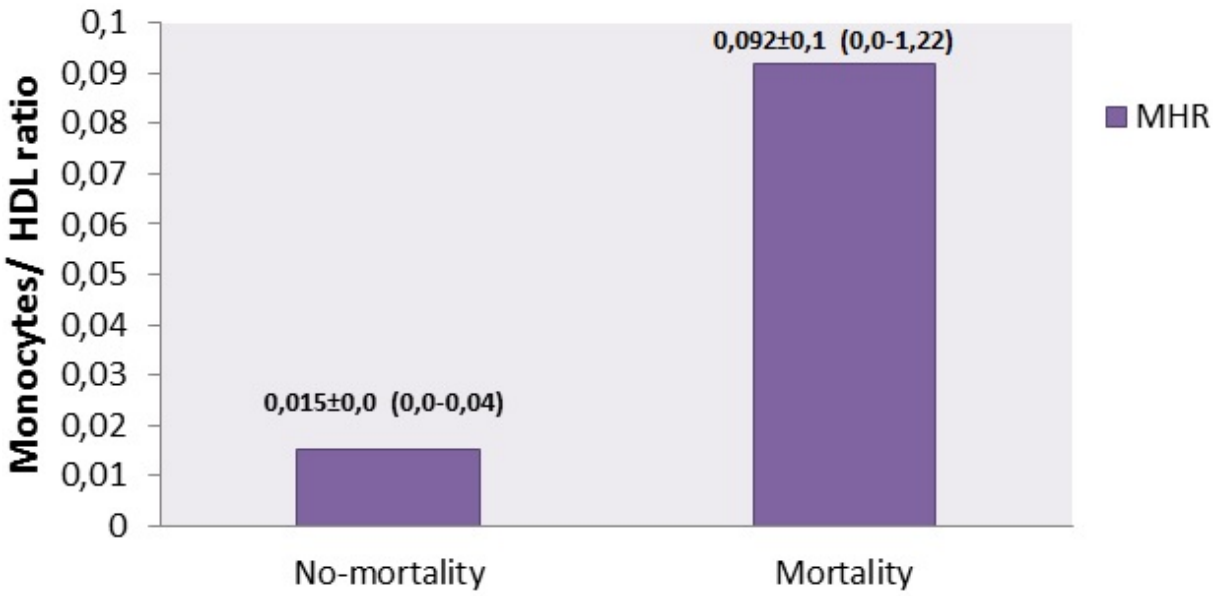

Figure 2: Comparison of MHR values between patients with and without PE mortality. Monocytes/HDL ratio seems influentially to be predicting survivability.

Discussion

In this study, we investigated the relationship between MHR, which is among readily available laboratory markers, and the severity of PE. Acute PE is a disease with significant morbidity and mortality. Studies have reported the rate of mortality due to PE between 8% and 30%. In our study, 59 (36.8%) patients died in the hospital. 43 (71.2%) of the deceased patients were massive PE patients. We think that a higher rate of mortality in our study compared to the literature resulted from the larger number of patients with massive PE.

The most widely recommended mechanism in order to explain the relationship between PE and hematological parameters is inflammation. Inflammation plays a primary role in the pathophysiology of PE. In inflammatory diseases, monocytes counts increase, while HDL-C levels decrease. Monocytes are a distinct type of leukocytes, migrate to the tissue macrophages and initiate inflammation. Previous studies have found that monocyte count is associated with the prediction of coronary artery Disease (11). On the other hand, HDL-C inhibits the activation of monocytes, prevents the transformation of monocytes to macrophages and decreases inflammation. In conclusion, the combination of these two parameters as MHR is thought to represent an inflammatory process. This relationship between monocytes and HDL-C has led researchers to investigate whether MHR is more effective than monocyte count or HDL-C alone in predicting cardiovascular events. Kanbay et al. reported that MHR acts as an independent predictor for cardiovascular events and increases in parallel with the decrease in eGFR in patients with chronic kidney disease (12).

It has been proposed that MHR is associated with systemic infection and endothelial dysfunction, and it can be used as a novel inflammation-based diagnostic and prognostic marker in cardiovascular diseases. In a study by Pamukcu, MHR was associated with mitral annulus calcification (13). In a study by Zhu et al. preoperative MHR value was significantly

higher in patients who developed acute deep vein thrombosis following total joint arthroplasty (14). In our study, there was a positive correlation between MHR values and cancer, Deep vein thrombosis, and chronic renal failure. However, there wasn't any correlation between MHR values and coronary artery disease, heart failure, hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular disease, atrial fibrillation, and COPD. In a study investigating prognostic value of MHR in predicting short term mortality in patients with acute PE, 26 of 99 patients (25.2%) died within the first month of the diagnosis and MHR was found to be significantly higher in these patients. The authors found that MHR was an independent predictor of mortality in patients with acute PE (15). In our study, 59 of 160 patients (36.8%) died after diagnosis of PE and MHR was found to be significantly higher in these patients. However, MHR was an independent predictor of mortality in patients with acute PE (B: 1.393, 95% CI (0.707-2.079), p=0.000) in our study. In the present study, we evaluated the correlations of MHR with the severity of PE and other variables. We found that the severity of PE, HDL, LDL, Total cholesterol, White Blood Cell, Neutrophils, Monocytes, CRP, Albumin, Neutrophil/lymphocytes ratio, and sPAB increased as MHR increased. Nevertheless, because the number of studies investigating the predictive value of MHR in acute PE is limited, our findings should be evaluated with further multicenter comprehensive studies.

Limitations of Study

This study has several limitations. The study was designed as an observational, retrospective and single-center study. In addition, repeating MHR measurements with certain intervals possibly would affect the results. We could not compare MHR with the other markers used in pulmonary embolism. Finally, we could not make a comparison between the patients using statins and those not using in order to avoid the confounding effect of statins on HDL-C values. Further comprehensive studies are needed to better clarify this relationship.

Conclusion

In conclusion, Monocyte-to-HDL-cholesterol ratio, which is an inexpensive marker easily available in all centers, can be used in acute pulmonary embolism for PE severity status and mortality status.

Conflict of interest

The authors declare that they have no competing interests with regards to authorship and/or publication of this paper.

Acknowledgment

Authorship Contributions: Idea/Concept and design; SK, EO, control/supervision; SK, EO, data collection and/or processing; SK, EO, analysis and/or interpretation; SK, literature review; SK, EO, writing the article; SK, EO, critical reviewing; SK, EO. There are no funding sources.

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Clinical Presentation and Frequency of Klatskin Tumor; A Single-center Retrospective Study

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Abstract

Klatskin tumor is an epithelial bile duct tumor that originates from the main hepatic duct or the right-left intrahepatic duct and appears proximal to the opening of the cystic duct. In this study, we examined the demographic characteristics, clinical, laboratory and radiological results at the time of first presentation of patients who were diagnosed with klatskin tumor in our clinic for a period of three years. For the study; 16 patients who were hospitalized at Internal Medicine Clinic between June 1, 2015-May 1, 2018 were diagnosed with Klatskin tumor were included retrospectively. Clinical, laboratory and radiological data of patients were analyzed. 16 patients in the study, 10 were male, 6 were female. Average age was 62.30 for males, 65.33 for females. The most common symptoms respectively jaundice, itching, abdominal pain, anorexia and weakness. Among the laboratory tests, the average of some values; AST:141.31 U/L, ALT:156.18 U /L, ALP:692.07 IU/L, GGT:622.14 U/L, T. Bilirubin:10.42 mg/dl, D. Bilirubin: 6.0 mg/dl, WBC:10.509 x103u/L. diagnostic ERCPs of the patients were examined; Klatskin tumor was considered in 14 patients due to stenosis in the proximal part of the common bile duct. Clinical and laboratory findings in Klatskin tumors are not specific and the diagnosis is usually made in the late period because the clinical presentation of the disease is confused with many other diseases.

***Key words**: Klatskin Tumor, Cholangiocharcinoma, ERCP, Clinical Presentation.*

Introduction

Cholangiocarcinomas (CC); are malignant tumors that make up 10-20% of all hepatobiliary malignancies and originate from bile duct epithelial cells (1). CC are classified according to their localization as intrahepatic, hilar and distal CC (2).

Klatskin tumor is a biliary tract tumor originating from the main hepatic duct or right-left intrahepatic duct and seen proximal to the opening of the cystic duct. Klatskin tumor is the most common tumor in the biliary tract and accounts for 60% of all CC (3). The annual incidence of Klatskin tumor is not more than 1: 100,000, and it is a rare type of tumor (4).

Among the etiological risk factors for the development of CC, Primary Sclerosing Cholangitis (PSC), some parasitic infections of the liver (Clonorchis sinensis

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and Opisthorchis viverrini) and hepatolithiasis are the best known. However, no etiological factor can be detected in the majority of patients (5).

Clinical manifestations in Klatskin tumors are usually those that develop due to obstruction in the bile ducts, such as jaundice and light-colored stools. In addition, symptoms compatible with malignancy such as loss of appetite, cachexia and fatigue may also be seen. Approximately 10% of the patients are accompanied by cholangitis at the time of diagnosis (7).

Among the laboratory findings of Klatskin tumor, there may be increases in carbohydrate antigen (CA-19-9) and Carcinoembryogenic antigen (CEA) levels. However, they are not specific for diagnosis because they increase in many diseases other than Klatskin tumor. Again, among laboratory findings, there is an increase in cholestasis marker enzyme levels produced in the liver depending on the localization and size of the obstruction created by the tumor in the bile ducts (8).

From the radiological imaging methods of Klatskin tumors, Hepatobiliary ultrasonography (USG) the presence of dilatation in the intra and extrahepatic bile ducts and a mass or obstruction in the bile duct can be shown. Computed Tomography (CT), Magnetic Resonance Cholangiopancreatography (MRCP) and Endoscopic Retrograde Cholangiopancreatography (ERCP) are used in both diagnosis and staging (8, 9).

Surgical resection is the only curative treatment option for early stage tumors in Klatskin tumor. Therefore, early diagnosis of patients is extremely important for survival. The current approach in surgical treatment is radical surgical resection, which usually includes choledectomy, hepatectomy, and portal resection (10).

Materials and Methods

This study was started after the approval of the ethics committee with the date 18.02.2021 and reference number 2021/03-03. A total of 16 patients who applied to our Internal Medicine Clinic between 1 June 2015 and 1 May 2018 and were diagnosed with Klatskin tumor were included in the study. The study was conducted in a single center by retrospectively analyzing the patient data previously recorded with standard data collection forms. Patients with a diagnosis of malignancy other than Klatskin's tumor were excluded from the study due to the possibility of metastasis to the bile ducts. Age and gender of all patients, symptoms at first admission, laboratory tests of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Gamma Glutamyl Transferase (GGT), Total Bilirubin, Direct Bilirubin and Leukocyte (WBC) parameters. and mean values were calculated and analyzed.

Again, among the radiological imaging methods performed at the first application of the patients, Hepatobiliary ultrasonography, all abdominal CTs and ERCP findings were examined. The results were statistically analyzed.

Statistical Analyses

Statistical package program SPSS 22 (Statistical Package for the Social Sciences, version 22, SSPS Inc, Chicago, IL, USA) was used for data analysis.

Results

Of the patients included in the study, 10 (62.5%) were male and 6 (37.5%) were female. The mean age of the male patients

was 62.30 (46-80), the mean age of the female patients was 65.33 (48-85) and the general avarage of age was 62.68.

When the symptoms of the patients during the first application were questioned, it was stated as; jaundice, itching, abdominal pain, loss of appetite and weakness.

Some laboratory tests of the patients in our study, which were checked at the time of the first application, were analyzed. Their mean values were respectively; AST: 141.31 U/L, ALT: 156.18 U/L, ALP: 692.07 IU/L, GGT: 622.14 U/L, T. Bilirubin: 10.42 mg/dl, D. Bilirubin: 6.0 mg/dl, WBC: 10509 x103 u/L.

When the hepatobiliary USGs of the patients were examined during the first application, Intrahepatic bile ducts were seen to be dilated in 16 patients, In 10 patients, dilatation was detected in the proximal part of the common bile duct. A mass was detected at the level of the bifurcation of the main hepatic duct in 3 of these patients. An appearance compatible with liver metastasis was observed in 2 patients.

When the abdominal CT scans of the patients included in the study at their first application were examined, Dilatation of intrahepatic bile ducts was observed in 16 patients, Concomitant dilatation of the extrahepatic bile ducts was detected in 1 patient. A mass was detected at the level of the main hepatic duct bifurcation in 7 patients, mass lesions compatible with liver metastases were observed in 5 patients, and in 2 patients, a mass was detected in the uncinate process of the pancreas.

When the ERCPs of all patients in our study made during the first application were examined, in 14 patients, stenosis in the proximal part of the common bile duct and dilatation in the intrahepatic bile ducts were observed, and the preliminary diagnosis of Klatskin tumor was considered in these patients. Irregular filling defect in the common bile duct and dilatation of the intrahepatic bile ducts were detected in 1 patient. In 1 patient, dilated common bile duct was observed, irregular filling defect in the hilar region and dilatation in the intrahepatic bile ducts were detected.

Discussion

CC is a malignant tumor arising from epithelial cells of the bile ducts. They originate from different parts of the bile tree, so they are classified according to their localization. They are classified as intrahepatic, perihilar and distal cc according to their anatomical locations (2). The most common of these is hilar CC so Klatskin tumor with approximately 60% (11). The reason why Klatskin tumor is very rare is that it does not cause symptoms in the early stage and laboratory findings are nonspecific, so the diagnosis is usually made at an advanced stage. Therefore, in this study, we aimed to examine the clinical presentation of Klatskin tumor.

Klatskin tumor usually occurs in advanced ages, most of the patients are 60 years and older (12). In our study, the mean age of the patients was similarly 62.68 years. This disease is seen at similar rates in both sexes, but in some studies it is stated that it is more common in men (13, 14). Similarly, in our study, it was found that it was more common in males.

Clinically, Klatskin tumor is usually asymptomatic in its early stages, so patients are usually diagnosed late. The most common symptom is jaundice, which is seen in approximately 90% of patients (11). Other common symptoms except

jaundice are fatigue, weight loss, itching and abdominal pain (11, 16). Similar to the literature, the most common symptoms in our study were jaundice, itching, abdominal pain, loss of appetite and weakness respectively. In addition, cholangitis was considered in 3 patients due to the presence of icterus, leukocytosis and fever at the first admission. The rate of cholangitis in the patients in our study was determined as 18.75%. This rate was evaluated as slightly higher when compared with the literature data (7).

There are no specific laboratory tests used in the diagnosis of Klatskin tumor. Biochemically, in the diagnosis of the disease, there may be an increase in serum carbohydrate antigens CA-19-9 and CEA levels. In addition, increases in AST, ALT, ALP, GGT and Bilirubin values can be detected (17). In our study, the CEA and CA19-9 values at the first admission of the patients could not be reached, but significant increases in AST, ALT, ALP, GGT and bilirubin values measured at the diagnosis stage were found. The increases in these enzymes produced by the liver were significant because they showed the picture of cholestasis in the patients. The presence of cholestasis was not detected in only one patient at the first admission.

Hepatobiliary USG has a limited place in the diagnosis of Klatskin tumor in radiological imaging methods; therefore, it cannot be recommended for surveillance or diagnosis (18). In our study, all patients were evaluated with hepatobiliary USG at the time of first admission. Dilatation of the intrahepatic biliary tract was detected in 16 patients, concomitant dilatation of the common bile duct was observed in 10 patients, and a mass was detected at the level of the main hepatic duct bifurcation in 3 of these patients. In addition, lesion compatible with liver metastasis was observed in two patients. Our results, in parallel with the literature studies, support the low value of hepatobiliary USG in the diagnosis of Klatskin tumor.

Conventional CT has an accuracy rate of approximately 70% in the diagnosis of Klatskin tumors. Therefore, its use is limited in the diagnosis of Klatskin tumor, and its main purpose is to determine the extent of extrahepatic disease (19). In the analysis of the conventional CT findings of the patients in our study taken during the first application period, only 7 patients had a mass at the level of the bifurcation of the main hepatic duct. In addition, findings compatible with liver metastasis were observed in 5 patients, and a mass in the pancreatic uncinate process was observed in 2 patients. These results we obtained were correlated with the literature data stating that the accuracy rate of conventional CT in the diagnosis of Klatskin tumor is low.

ERCP can show direct mass and dilated bile ducts in the diagnosis of Klatskin tumor. At the same time, ERCP is the most valuable method for the diagnosis of Klatskin tumor because it allows the collection of brush swab samples from the bile ducts for cytological examination (20). In our study, as a result of the first ERCP procedures of the patients, stenosis in the proximal part of the common bile duct and dilatation in the intrahepatic bile ducts were detected in 14 patients. Irregular filling defect in the common bile duct in 1 patient, dilated common bile duct in 1 patient, irregular filling defect in the hilar region and dilatation in the intrahepatic bile ducts were detected in both patients.

When Klatskin tumors are detected at an early stage, surgical resection is the most effective treatment option for long-term

survival and cure (21). Orthotropic liver transplantation can be performed in diseases such as liver cirrhosis and primary sclerosing cholangitis which are not suitable for surgical resection (22). Chemotherapy and radiotherapy are used in the treatment of patients with advanced or inopreable Klatskin tumor, but their effects on survival alone are unfortunately limited when compared with complete surgical resection (23).

Conclusion

The incidence of Klatskin tumor has increased significantly in recent years. However, diagnosis is still delayed due to the non-specific clinical presentation. Early diagnosis is extremely important as the only cure is surgical treatment. For this reason, early diagnosis of patients by using imaging methods without wasting time in case of clinical suspicion will positively affect both the chance of cure and survival.

Limitations of the study

The limitations of our study and the small number of patients in our study are because of the fact that it was conducted in a single center, and the treatment options of the patients after the diagnosis and the duration of survival are not known. For these reasons, we believe that multicenter studies with larger patient series are needed to obtain more detailed information about Klatskin tumor.

Conflict of interest

The authors declare that they have no competing interests with regards to authorship and/or publication of this paper.

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Review Article

The Miraculous Nutrient: Human Breast Milk

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Abstract

Breastfeeding gives every child the best possible start in life. It is very beneficial for both children and mothers in terms of health, nutrition and emotionality. Moreover, it forms part of a sustainable nutrition system. Human breast milk is the miraculous nutrition source that contains all the nutrients needed for the normal growth, development and protection of newborns from diseases. In addition to the benefits of human breast milk for the baby, it is known that it has many benefits in terms of attachment, mental health, behavioural effects and the mother in the long and short term.

***Key Words*:** *Breastfeeding, Human breast milk, Infant nutrition.*

1. Introduction

Human breast milk is the most beneficial source of nutrients in terms of nutritional, hygienic and economic aspects compared to other foods, and it has a very special biological and emotional effect (1). It contains all the nutrients needed for the normal growth, development and protection of newborns from diseases (2). In the Convention on the Rights of the Child adopted by the United Nations General Assembly (UNGA) in 1989, it was emphasized that "all segments of the society should be informed about breastfeeding, supported and provided with educational opportunities in this field" and "breastfeeding is the human right" (3). This review was made to address the content of human breast milk and to examine the benefits of human breast milk in many other aspects for the mother, child and the society. Especially by drawing attention to the importance of human breast milk in the first six months, it will enable mothers to be much more conscious in the postpartum period. Therefore, the mother, baby and the society will benefit from the benefits of human breast milk at the highest level, thus contributing to the realization of qualified breastfeeding.

2. Material and Methods

The data in this review were searched through the Cochrane Library, EMBASE (OVID), Pub Med, Web of Science, Google Scholar and WHO Global databases. The keywords "Human Breast Milk", "Breastfeeding", "Breast Milk" and "Lactation" were used during the investigation.

3. Human Breast Milk in the History

When the historical development of the practices related to infant nutrition was

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examined, it has been seen that the most important nutrient in infant nutrition until today has been human breast milk. It was emphasized that in the Ebers Papyrus (Ancient Egypt 1550 BC), one of the historical works, the only nutrient to be used in infant feeding is human breast milk and that the baby should receive human breast milk until the age of three (4,5). Babylonians (Mesopotamia), who attached great importance to breastfeeding, depicted their chief god Ishtar, when she was breastfeeding her baby. In Yakut Turks, who believed in the sanctity of human breast milk, we can come across the beliefs that Ayzıt, the mother goddess, revived her baby by giving human breast milk. Similar beliefs have increased with the emergence of the religion of Islam, and according to Islam, there is a connection between the mother's nutrition and the infant's breastfeeding (4).

In the books written in Europe during the Renaissance, it was stated that human breast milk was the most ideal nutrient for babies. However, the inclusion of women in working life with the industrial revolution in Europe in the 20th century led to a decrease in the interest in breastfeeding and the spread of untrue practices such as social change movements and the transformation of bottle-feeding into the symbol of modern motherhood (5). After the 1970s, the focus of research on human breast milk and the increasing number of studies until today have emphasized that human breast milk is a unique nutrient, and it is very important for infant nutrition. While the rate of breastfeeding was 24.9% in the 1970s, today this rate has increased by 3-4 times. This increase is undoubtedly due to the fact that experts in various fields of science have internalized the importance of the benefits of breastfeeding (4). While the use of human breast milk is increasing rapidly in the world, the same is true for our country. According to the Turkey Demographic Health Survey (TDHS-2018) conducted in our country, the breastfeeding rate and duration were given in Figure 1 (6).

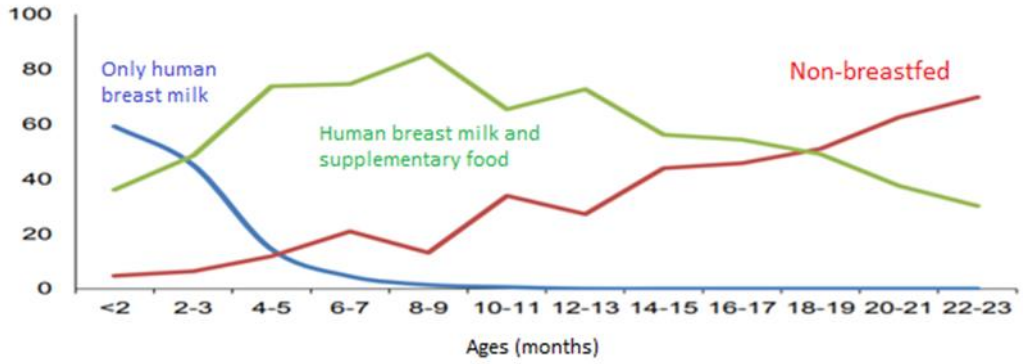

Figure 1. The breastfeeding practices and the percentage distributions of children under 2 years old (TDHS-2018).

4. Human Breast Milk in terms of Nutritional Value

The most important feature of human breast milk content is that it varies according to the age and condition of the baby. For example, mothers who gave birth prematurely secrete milk suitable for the weight of their babies, gestational week

and kidney solute loads (7). The difference between the breast milk of premature and term mothers disappears after the first month. In the period from birth to the first month, the content of human breast milk (in terms of nutritional elements) varies in accordance with the baby's digestive system (7,8). The content of human breast milk is complex, it contains multiple supplements, and they vary widely. The density of some nutrients can also differ between women, during breastfeeding and throughout the day (7). Changing the content of human breast milk allows it to adapt to meet the baby's ongoing need. In addition, changing diet potentially stimulates sensory development, and it allows for better acceptance of new nutrients and flavours (8-10).

4.1. The Content of Human Breast Milk

Human Breast milk can be examined in two parts as nutritional content and bioactive content (11).

4.1.1. Nutritional Content

4.1.1.1. Macronutrients

Approximate amounts of protein, fat, lactose and energy content of mature term human breast milk were given in Table 1 (12).

Table 1: Content of Mature Term Breast Milk by Essential Nutrients.

Macronutrients	
Protein	0.9-1.2 g/dl
Fat	3.2-3.6 g/dl
Lactose	6.7-7.8 g/dl
Energy (kcal)	65-70 kcal/dl

The Composition of Human Breast Milk Protein

The high ratio of whey: casein (60:40), whey proteins both facilitates digestion and the substances that prevent infection in the whey section that protects the baby against the diseases. Although human breast milk carries a lower level of protein than cow's milk, it creates the ideal protein structure by providing adequate tryptophan level and appropriate amino acid storage in the infants due to its richness of protein content in whey protein and alpha-lactalbumin (12).

The Oils of Human Breast Milk

The baby's main energy source is comprised of oils. Both the high ratio of unsaturated fatty acids and milk lipase make digestion easy and fast. Large amounts of long-chain fatty acids in human breast milk are beneficial for both brain and eye development (10).

The Carbohydrates of Human Breast Milk

Lactose, which is the main carbohydrate source of human breast milk, facilitates calcium absorption, provides the necessary energy for brain development and prevents the growth of harmful microorganisms in the intestine (9).

Major changes occur in the content of human breast milk in the first month after birth. While there may be differences between mothers, it also varies between the baby's gestational week, postnatal age and the beginning of breastfeeding (9-11).

Term Milk/Premature Human Breast Milk

In the first weeks, human breast milk, which is provided by a mother who gave a premature birth, has a higher level of protein, fat and sodium than term human breast milk. The difference disappears in the following weeks (12).

Colostrum

It is the milk that is secreted in the first

five days after birth and whose amount, appearance and content are different. It is yellowish in color and secreted in small amounts. Colostrum facilitates the outflow of meconium with its laxative and protein degrading effect and prevents meconium ileus. It is also described as the baby's first vaccine (13).

- It has the antibodies and white blood cells that protect from diseases and allergies, Secretory IgA, lactoferrin, macrophages. It is rich in factors that prevent infection such as T and B lymphocytes.
- It contains epidermal growth factors that provide maturation of the intestine and prevent the development of allergies and intolerances.
- Vitamins A, D and B12, sodium and zinc content are higher than mature human breast milk.
- It protects against jaundice by allowing bilirubin to be expelled from the intestine.
- The low lactose content indicates that its main function is immunological and trophic, not nutritional.
- Colostrum reflects the general structure and properties of maternal blood. This physiological similarity is an advantage for the newborn who is accustomed to intrauterine life. Gradually, there are differences in the content of milk and it reaches the grade of mature milk within 15 days (11).

Transitional Human Breast Milk

It is the milk secreted between five days and two weeks after the birth. Its amount is higher than colostrum. While the protein content decreases, the lactose, fat, and calorie contents increase.

Mature Milk It is the milk secreted two weeks after the birth. Human breast milk gains a fully mature milk feature in postnatal 4^{th}-6^{th} weeks.

Foremilk-Hindmilk

High carbohydrate milk is secreted at the beginning of breastfeeding, and high-fat milk is secreted at the end. It is difficult to predict when this change occurs in the breastfeeding process; however, what is important is that the baby should discharge the breast and leave the breast spontaneously in order to provide all the needs of the infant and to regulate the milk secretion cycle. In this case, the infants can take the oil-rich hindmilk (11,12).

4.1.1.2. Micronutrients

The micronutrient content of breast milk varies according to the mother's diet and storage (such as vitamins A, B1, B2, B6, B12, D and iodine). Since the mother's nutrition is not always very good, multi-vitamin supplements are recommended to the mother during breastfeeding. Since the amount of vitamin K in milk is very low regardless of maternal nutrition, 1 mg of vitamin K should be given IM to each newborn. However, vitamin D is also low in breast milk, so it is recommended to take early supplements. The iron content of breast milk is low, and iron deficiency anemia is rarely seen in the first 6-8 months in babies who are fed with breast milk alone and whose umbilical cord is clamped late, since its absorption is very high (9).

4.1.1.3 Water Content and Taste The water content of human breast milk is high, and there is no need to give additional water as long as the baby is breastfed whenever he wants, even in the hottest weather. The taste of human breast milk differs according to what the mother eats. These changes in taste make it easier for the baby to adapt to the taste of the food eaten in the

baby's family and to switch to additional nutrients after the sixth month (14).

5. The Importance of Human Breast Milk in terms of Infant Health

The purpose of infant nutrition is to meet basic nutritional needs and to support growth and development. Human breast milk is the main food for the baby from birth to one year old, and its importance lasts until the age of two (15). The organizations such as the World Health Organization (WHO), the American Academy of Paediatrics (AAP), and the United Nations International Children's Fund (UNICEF) recommend starting breastfeeding within the first half hour after birth and providing only breast milk for the first six months. They also state that it would be good to continue breastfeeding from the first six months along with nutritional supplements until the age of two and above (16). According to the American Dietetic Society, breastfeeding during the first six months of life is the most suitable nutrition for babies, and it is very important for the protection of health. In addition, breastfeeding has important contributions to public health such as improving and maintaining newborn health, reducing morbidity, mortality and health care expenditures (15, 16).

The perfection of mother's milk, which is a unique natural food suitable for the offspring of every living creature, is due to the fact that it provides the growing organism with the nutrients that are needed with the changing content. While breast milk contributes to the healthy growth and development of babies, it also plays an important role in establishing and strengthening the bond between mother and baby (17). The studies have shown that bacterial meningitis, sepsis, diarrhoea, respiratory tract infection, severe gastrointestinal infection, middle ear infection, urinary tract infection in babies who are not breastfed, and that the incidence and severity of late-stage infections in preterm babies are higher (17-19). In addition, according to a study, it was reported that the prevalence of premature retinopathy was higher in premature babies who were fed with infant formula instead of human breast milk (18).

Furthermore, several studies have shown increased rates of sudden infant death syndrome in the first year of life, as well as diabetes mellitus in older children and adults who were formula-fed compared to those who were breastfed; childhood cancers such as leukaemia, Hodgkin's disease and lymphoma; an increase in the incidence of obesity, asthma and high cholesterol levels (20, 21). There is some evidence to suggest that the breastfed babies are not only healthy, but also tend to be smarter. Various studies on intelligence development in the infants have shown that infant formula feeding is associated with lower intelligence performance (22).

6. The Advantages of Breastfeeding for the Maternal Health

Feeding babies only with breast milk in the first six months of life, continuing breastfeeding with additional nutrients after the sixth month and continuing breastfeeding until the age of two provide numerous benefits for both the baby and the mother (23).

When skin-to-skin contact between mother and baby is facilitated by breastfeeding, the risk of late postpartum haemorrhage in the mother is considerably reduced. Oxytocin is a natural method of preventing postpartum haemorrhage following delivery (24). Women who have not

menstruated six months after birth, who do not regularly supplement with infant formula, who do not exceed four hours during the daytime breastfeeding period and six hours during the night breastfeeding period, have a less than 2% chance of conception (25). In addition, mothers who breastfeed often return to their pre-pregnancy weight faster than mothers who do not breastfeed. Breastfeeding has another long-term positive effect on women's health. Women who do not breastfeed have an increased risk of developing both breast and ovarian cancer later in life. From a psychological point of view, breastfeeding also promotes the feeling of motherhood; it is a natural sedative for the mother and strengthens the bond between mother and baby. Breastfeeding mothers are more self-confident, which also positively affects the milk yield (21).

7. Conclusion

Various policies are developed in the world and in our country regarding human breast milk, which is so valuable. Promoting human breast milk with the project initiated by the Ministry of Health and UNICEF as "Baby-Friendly Hospital" has provided a social motivation. In addition to all these benefits, the fact that a nutrient equivalent to human breast milk has not been produced until today reveals that human breast milk is indispensable and an excellent nutrition for the newborn.

It is recommended that pregnant women attend the antenatal education sessions. It is also suggested to draw attention to human breast milk and breastfeeding in these trainings, inform mothers about the content and benefits of human breast milk, and encourage them to breastfeed their babies.

8. Conflict of Interest

There is no conflict of interest between the authors.

9. Acknowledgement

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Review Article

Hypnosedative Drugs and Alcohol Consumption: Case Report and Literature Review

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Abstract

Besides of abuse alcohol consumption, abuse of hypnosedative drugs is unsettingly common. As a result of concomitant consumption of these substances together, undesirable side effects such as decreased reasoning ability, blurred consciousness, decreased reflexes and death appear in the clinic. In this review, when alcohol and benzodiazepine are used together, the physiological absorption processes of these chemicals and the factors affecting their distribution in body tissues are discussed.

Key words: *Alcohol, Hypnosedative drugs, Abuse, Concomitant consumption.*

1. Introduction

Alcohol is one of the most commonly abused substances in the world. The sedative effect of alcohol on the central nervous system may vary according to the type and amount of alcohol consumed, drugs taken at the same time with or just before or after alcohol consumption, foods and individual factors. In contrast to limited alcohol consumption, increasing doses of alcohol are associated with numerous adverse effects on physiological and neuropsychological mechanisms.

Benzodiazepines are an important type of hypnosedative drug with the potential for abuse. Among the clinical indications of benzodiazepines are anxiety disorders, convulsions, muscular rigidity, insomnia, and preoperative medication. Benzodiazepines have now begun to replace barbiturates, another group of hypnosedative drugs often used in the past. Because benzodiazepines do not have an addictive effect as barbiturates, but they can cause sedation at least as much as they do. They show their effects through gamma-aminobutyric acid – A channel (GABA – A) which transmits anions after binding GABA, an effective inhibitory neurotransmitter in the central nervous system (CNS).

Any concomitant use of benzodiazepines and alcohol, which have sedative properties on the CNS, carries risks of overdose, a more severe reduction in cognition and reflexes, a greater potential for side effects, and increased potential for unpredictable outcomes that may accompany acute states or long-term results.

In this article, chemical analyses reports of body samples obtained from individuals who died after a fall from height accident were investigated. Those reports which

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have been providing information about probability of having been used alcohol before death, in which way the substances detected in blood samples had been taken into the body, the observable effects of the substances on human body, how the fatality influences transformation of the substances, factors that may affect the distribution in various tissues where the samples had been obtained from, and possible effects of end products at determined doses, were discussed in this article.

Case Report

A 37-year-old patient was reached after getting trapped under a roble for 34 hours due to falling from height. Various body fluid samples were taken and sent to laboratory for analyses. In chemical analyses, 10 g of liver tissue, 10 g of kidney tissue and10 ml of stomach content were examined. Accordingto the final report, blood sample was found to contain (91 mg/dl) ethanol, (143 mg/dl) methanol, no formic acid, vitreous humor neither ethanol nor methanol, and liver and stomach contents nordiazepam (14 ng/ml) and diazepem (<1 ng/ml). Also, it is stated that there was some food residue, but no other substances could be detectable with the relevant laboratory systematics.

2. Discussion

Ethanol (ethyl alcohol) belongs to the group of chemical compounds known as alcohols. These compounds consist of carbon, hydrogen, and oxygen molecules arranged in specific configurations, giving them specific properties such as solubility in water and lipid (oil) and volatility (ease of evaporation). Ethanol (C2H5OH), one of the flammable organic compounds, is the only type of alcohol found alcoholic beverages. During manufacture of alcoholic beverages, microorganisms called yeast are added to the sugar–containing medium, and alcohol is produced by the fermentation method.

Blood alcohol concentration (BAC) is measured in humans for medicolegal and forensic purposes. It is widely known that the higher level of ethanol in circulation the more deteriorated physical and cognitive performance. In daily practice, blood alcohol level and blood ethanol level are used synonymously. The use of ethyl alcohol as a drink creates important forensic problems. Beer obtained by fermentation contains 4-8% of alcohol by volume, wine 9-14%, and beverages such as raki, vodka, gin, rum, brandy, whiskey obtained by distillation method contain 35-45% of alcohol (1).

Positive ethanol in body samples taken after death can be interpreted as important evidence that the person consumed alcohol exogenously (externally) before death. It should not be overlooked that after death, there are factors that can lower the level of alcohol consumed before death (false miscarriage). In addition, there are situations that may cause high alcohol levels in tissue samples taken after death, even without alcohol consumption before death.

The equilibrium concentration of alcohol in a tissue depends on the water content of that tissue. The stabilization of alcohol in a tissue depends on its water content, blood flow rate, and tissue mass size. Ethanol has properties similar to water, insoluble in fats and oils, but can pass through biological membranes. Ethanol is distributed from the blood to all tissues and fluids in proportion to the amount of water they contain. Based on this information, the same amount of alcohol consumed per body weight may cause different levels of blood alcohol

concentration values to be measured in different individuals. These differences are due to the changes in the fat and water ratios in body composition of people. The most obvious example of this situation is higher blood alcohol levels are encountered in women compared to men, despite consuming the same amount of alcohol. In addition, due to the faster first–pass metabolism of alcohol through stomach of men, the blood alcohol level may be lower during absorption (2-3). In other words, if there was an early death in the absorption phase after drinking alcohol, the alcohol level, which is likely to reach higher levels, may have been determined relatively low.

Many factors have been identified that affect alcohol absorption. Absorption of alcohol in the duedonum and jejunum (regions of the small intestine) is faster than in the stomach. Thus, the rate of gastric emptying is an important determinant of the rate of absorption of orally ingested alcohol. The various factors that affect alcohol absorption and therefore the level of ethanol measured in the blood are as follows; 1) Alcohol crosses biological membranes by passive diffusion. Therefore, the higher amount of alcohol consumed, the faster it is absorbed into the body. 2) If the blood flow in the intestinal region through where alcohol is absorbed is sufficient, it will increase the absorption of alcohol. In case of premature death, alcohol absorption will stop. 3) Alcohol is an irritating molecule. If taken in high concentrations, it can cause bleeding and superficial erosion (destruction) in the smooth muscle layer of the stomach. This may reduce alcohol absorption. 4) If the ethanol consumed is taken at once rather than in many small doses, the level of blood alcohol level may be higher. 5) Presence of food in the stomach delays gastric emptying and therefore reduces the absorption of alcohol, which is associated with the concept of “should not be consumed on an empty stomach”. The most important factor determining the rate of alcohol absorption is whether the beverage is taken on an empty stomach, with meals, or after meals.

10-20% of the alcohol consumed orally is absorbed from the stomach and mixes into the blood. The remaining (80-90%) part is absorbed from the small intestines and mixes with the blood. The majority of alcohol absorption occurs in the small intestines because of the large absorption surface and high blood flow velocity of this region. For this reason, the rate of alcohol absorption may vary depending on the rate of gastric emptying and adequate blood supply to the intestines. The time elapsed after alcohol consumption is one of the most important determinants of the amount of alcohol consumed, which can be absorbed from the intestines and cause a significant difference in the level of alcohol mixed into the blood. The absorption phase continues as long as alcohol is consumed. The blood alcohol concentration (BCC) continues to increase until the maximum blood alcohol concentration (Cmax) is reached. According to the results of many controlled drinking experiments, the Cmax level is usually reached within 10-60 minutes after the last alcohol consumption. However, the factors described above show that the time to reach the Cmax level (tmax) in individuals consuming alcohol can shrink to 10 minutes if the stomach is empty, or extend up to 120 minutes in the presence of retarding factors (4). Some factors affecting the blood–alcohol concentration (BCC) or Cmax reached

after consumption of a certain dose of ethanol and their possible mechanisms are given in Table 1. In the light of this information, the blood alcohol concentration varies (lower or higher than it should be) depending on the amount of alcohol consumed, the oxidation (breakdown) rate of alcohol, drugs that affect the gastric emptying rate, and whether or not they are taken with food. The fact that there was food residue in the stomach contents in the autopsy report of the person supports that he ate recently.

Table 1: Some factors and possible mechanisms affecting blood–alcohol concentration (BAC) or Cmax.

Various variables or Alcohol consumption factors	Possible mechanism and/or explanation	Expected effect on BAC Level
Low body weight	Low body water	Higher BAC
Body fat level, high BMI*	Excess fat and decreased body water	Higher BAC
Female gender	Decreased body water	Higher BAC
Fast consuming	Fast absorption	Higher BAC
Consumption on an empty stomach	Rapid gastric emptying	Higher BAC
Consumption with/after meals	Delayed gastric emptying	Lower BAC
Alcohol consumption with high ethanol content	Fast absorption	Higher BAC
Low or decreased liver blood flow	Slow metabolism	Higher BAC
Smoking	Delayed gastric emtying	Higher BAC
Drugs that contract the pylorosphincter	Rapid ghastric emptying and absorption	Higher BAC
Drugs that delay gastric emptying	Slow absorption	Lower BAC
Gastric bypass surgery	Fast absorption	Higher BAC

Ethanol absorbed after the intestines reaches the liver via the portal vein system. Not all ethanol reaching the liver can be metabolized at once. Some ethanol continues to circulate in the blood without being metabolized. Because the alcohol dehydrogenase enzyme reaches saturation and ethanol is maximally metabolized at this saturation level. Ethanol is formed mainly by the effect of various biochemical processes and enzymatic activity in the liver (5). Some of the alcohol taken orally does not enter the systemic circulation, but can be oxidized by alcohol dehydrogenase (Types I and III) in the stomach. The efficiency of this first pass metabolism can regulate alcohol toxicity by determining alcohol bioavailability (intestinal absorption). Medications such as histamine receptor agonists such as cimetidine and ranitidine or drugs such as aspirin inhibit ADH activity in the stomach. This effect will also decrease the stomach's first–pass metabolism and therefore increase ethanol concentrations in the blood. The overall clinical impact of first–pass metabolism in the stomach is controversial. The rate of gastric emptying regulates the gastric and hepatic first–pass metabolism of alcohol. Considering the higher levels of alcohol metabolizing enzymes in the liver, it suggests that the liver plays the main role in alcohol metabolism (6-8) The enzyme mainly responsible for ethanol metabolism is alcohol dehydrogenase (Type I ADH),

which is found in the cytosol of hepatocytes and converts ethanol to a more toxic product, acetaldehyde. Fortunately, in mitochondria, acetaldehyde is rapidly oxidized to acetic acid. Acetate produced during the metabolism of ethanol leaves the liver and enters the Krebs cycle and turns into carbon dioxide and water in tissues outside the liver (9). As a result; 1) About 90% of the alcohol is removed by oxidation. 2) Most of this alcohol oxidation occurs in the liver. 3) Alcohol cannot be stored in the liver and is broken down into its metabolites. After the liver, it reaches the heart via the hepatic veins. After ethanol is transported from the right heart cavities to the lungs via the pulmonary artery, it returns to the heart. After the left heart cavities, it is pumped to the tissues through the arterial blood flow. The equilibration of ethanol between extravascular tissues and between tissues and blood depends on regional capillaries and blood flow per gram of tissue (10). Organs and tissues with a high blood flow per gram of tissue, such as the brain, liver, and kidney, are rapidly stabilized by the ethanol concentration in the arterial blood. This contrasts with equilibration in skeletal muscle tissues, and during the ethanol absorption phase (in the case of sudden death without equilibration) ethanol concentrations in arterial blood are expected to be approximately 40% higher than in venous blood. The reason for this is that when alcohol is absorbed from the stomach, it first goes to the arterial blood (11-13). It is not known where the blood sample was taken from in the case. In cases of delayed autopsy, it is known that in practice, samples are taken from the pooled blood in the abdominal cavity, intracardiac and intrathoracic regions. In the concrete case, if the person drank alcohol and a venous blood sample was taken while it was still in the absorption phase, the alcohol value might have been found to be approximately 40% lower.

In forensic toxicology, samples are taken from various body fluids to be examined during autopsy in order to determine whether alcohol and various drugs have been used. These are blood, urine, saliva, vitreous humor (intraocular fluid), cerebrospinal fluid, bile fluid and gastric contents. Vitreous humor (intraocular fluid) is a fluid located within the eyeball between the retina and the lens. This liquid does not contain cellular elements, has a gel–like consistency, is colorless, and consists of a large amount of water (over 90%), hyaluronic acid, collagen fibers (type II), inorganic salts and ascorbic acid. Since vitreous fluid is an isolated tissue that is relatively affected by post–mortem changes such as redistribution of chemicals in the body and increase in blood density, it is used in post–mortem examinations. However, although it is not a common situation, it should be kept in mind that in the case of structural disorders or diseases in the eye structure, the vitreous fluid results may be affected when interpreting. Alcohol metabolism in vitreous fluid is minimal. Therefore, although it is popular in the detection of alcohol use in forensic toxicology, the ethanol content of other body fluids should also be examined and interpreted together. If alcohol is detected in the vitreous fluid, it may be evidence that the person may have used alcohol before death. However, this transition requires a reasonable amount of time. It has been stated in various sources that ethanol may be positive in the vitreous fluid approximately 2 hours after oral (by mouth) alcohol intake (14). If ethanol is not detected in the vitreous fluid (that is,

during this period when the alcohol distribution in the tissues is not fully formed), it can not be said with certainty that the individual does not consume alcohol. When the literature is examined, there are many studies comparing the rates or levels of blood and vitreous liquid alcohol concentrations. However, the striking point in these studies is that the time between alcohol consumption and the moment of death in the examined corpses usually takes days. In a study of 295 people, alcohol was examined in vitreous fluid and blood analysis. In 27% of the cases (81 cases), blood alcohol concentrations were higher than the vitreous fluid concentration. In fact, in 24 of these 81 cases, alcohol was positive in the blood, while alcohol was negative in the vitreous fluid. The blood alcohol level of these cases in which alcohol was not detected in the vitreous fluid was also found to be in the range of 10-300 mg/dl (15). Although these data are rarely encountered in practice, it shows that in an individual who consumes alcohol before death, alcohol may not be positively detected in the vitreous fluid within the first 2 hours after the last alcohol intake.

Although 90% of ethanol is metabolized in the liver, 5-8% is excreted unchanged through respiration and in urine. Therefore, it is also possible to search for alcohol directly in the urine. However, in the present case, urine sample was not taken and the material content, which is an important evidence value, cannot be evaluated.

Alcohol can also be searched for in stomach content examination. In a person who has taken alcohol orally, there is a possibility that the stomach content sample will be positive only if it is sampled within the first few hours after alcohol intake (in the absorption phase). After death, the alcohol in the stomach quickly escapes from the stomach mucous membranes by diffusion method. As in the concrete case, it does not seem theoretically possible to detect alcohol positivity in the stomach content, when the delayed autopsy of a corpse found 33 hours after death and the time taken for the gastric content sample to be taken in this process are added.

In the concrete case, in the presence of many variable factors, it is necessary to examine the postmortem alcohol consumption markers that can concretely reveal the antemortem (pre-death) alcohol intake. About 1% of the alcohol consumed is metabolized in different ways. Ethyl glucuronide (EtG), ethyl sulfate (EtS), phosphatidylethanol and fatty acid ethyl esters (FAEE), which are minor metabolites of alcohol, are formed by these different metabolic pathways (16-20). Since forensic toxicology laboratories are not available in every city in our country, this opportunity cannot be applied in practice. Therefore, none of these markers were examined in the body fluids or tissues of the present case. If these parameters were examined and found to be negative, the claim that alcohol was not consumed before death could be supported. However, the fact that the aforementioned markers were not examined in this case cannot constitute a definitive judgment that the person did not consume alcohol before death.

It is also possible that the ethanol level decreases due to the consumption of microorganisms (In vitro alcohol consumption). Samples taken from body fluids should be kept in suitable conditions until the time they will be studied. Otherwise, the actual blood ethanol level can be measured lower. This can cause a

low blood ethanol level of someone who consumed alcohol before death. The cause of the described condition is usually contamination by microorganisms that metabolize ethanol in samples with other compounds. To minimize this problem, samples should be collected with suitable protective fluids and containers and stored at 4°C (21).

Alcohol can be detected in body samples by postmortem diffusion or contamination. Contamination occurs when the stomach or other hollow organ is disrupted, possibly by dispersal of ethanol-containing contents into other body cavities. If blood is taken from these cavities (for example, the chest cavity) during the autopsy procedure, a false elevation of the ethanol level may be detected. A peripheral vein, the femoral vein (inguinal vein), is a preferred site for the specimen as it is generally not affected by this condition.

Alcohol production after death is another challenging situation in forensic examinations. The ideal timing is to collect blood samples immediately after death for toxicological examination. Because after death, microorganisms both inside and outside the body can cause decay in tissues. They can produce alcohol from glucose (carbohydrate, sugar) by fermentation method by various bacteria and yeasts. This situation can be seen similarly in the human body. Glucose in the body is the raw material for these microorganisms to produce alcohol. A dead human body can create ideal conditions for these microorganisms. In general, it is known that corpses can produce alcohol within a few days of death under conditions of 20-25°C (22). Rapid decay may occur at temperatures above 20-25°C, but the highest and lowest temperatures were recorded as 20-8°C and 21-8°C within 48 hours encompassing the moment of the case we reported. Another point to be noted here is that these microorganisms do not only produce pure alcohol. Besides alcohol, butanol, 2-propanol, acetone and 1-propanol are produced (23-24). However, in the present case, the level of these molecules was not examined. According to the literature, the alcohol level produced by severe decay can reach 200 mg/dl. In the present case, the signs of decay are the larvae in the left eye and ear, and a slight discoloration of the liver, which can not be considered as signs of severe decay. In the experiences of the same authors, it has been explained that isolated post-mortem alcohol production may rarely increase the ethanol level above 60 mg/dl, and if the alcohol amount above 120 mg/dl is detected, this is due to antemortem (pre-death) alcohol consumption. (25-26). 91 mg/dl ethanol and 143 mg/dl methanol were detected in the blood of the concrete case, and a total of 234 mg/dl alcohol was detected.

Ethyl alcohol is a central nervous system depressant anesthetic. In alcohol poisoning, the frontal lobe of the brain is affected. This may cause decreased reasoning ability, coordination disorder in voluntary body movements and disorientation. Higher doses can cause drowsiness, followed by coma or death. Clinical findings are not always dependent on blood alcohol level. Tolerance to alcohol against high blood alcohol levels in chronic alcoholics may lead to the absence of an important clinical finding. People who do not have the habit of using alcohol and who do not develop tolerance to alcohol have more severe symptoms than normal. According to the data in the literature, motor coordination disorders (decrease/loss of voluntary control of the

musculoskeletal system) and judgment disorders, mood changes and deterioration in cognitive functions are expected due to the cerebellum (cerebellum) effect at a blood ethanol level of 80-200 mg/dl (27-30).

Another alcohol derivative that can be detected in postmortem analysis of body tissues and fluids is methanol. Methanol (CH3OH) is a simple alcohol and is obtained by distillation of sawdust. It is a colorless, volatile and toxic liquid. It is widely used in industry. For this purpose, it is used in the production of substances such as paint thinner, duplicator fluid, antifreeze, glass cleaner. Under normal conditions, it is not used in the production of alcoholic beverages, but methanol poisoning has been frequently encountered in our country recently.

Methanol is a highly toxic (poisonous) substance for the human body. While acute poisoning occurs mostly as a result of accidental use as a fake drink, chronic poisoning occurs as a result of inhalation (inhalation) of the vapor in the workplace. Apart from this, it is also possible to absorb methyl alcohol, which is abundantly contaminated with clothes, by absorption through the skin. The methyl alcohol that comes to the liver through the blood is first slowly converted to formaldehyde by the alcohol dehydrogenase enzyme and then to formic acid by the aldehyde dehydrogenase enzyme. However, this conversion takes place 5-10 times slower than the rate of conversion of ethyl alcohol. Therefore, if there had been fake alcohol consumption in the concrete case, the metabolite of methanol (formic acid), whose metabolism is much slower, might not have been at a level that could be measured in the blood because of the absorption phase. As mentioned in the previous sections, it will take 5-10 times longer than ethyl alcohol to mix with the blood, reach the liver, and be metabolized like ethyl alcohol in the absorption phase. It should not be expected to become positive in vitreous fluid. It is a situation that is frequently the subject of judicial cases where alcohol is used to reduce costs in bars or restaurants where alcohol is consumed or false alcohol is served by mistake. In this case, in addition to the presence of methanol detected in the blood of the case, the negative formic acid in the blood and vitreous fluid may be due to incomplete methyl alcohol absorption and insufficient metabolism due to the premature death of the case while still in the absorption phase of the fake alcohol (methyl alcohol), which may have been consumed orally may occur. In addition, except for methyl alcohol consumption, if blood samples are collected from outside the body with contaminated (contaminated) blood, this situation may also develop as a result of contact.

Benzodiazepines are a group of drugs that have sedation, hypnotic (sleeping), anxiolytic (anxiety relief) and muscle relaxant effects by binding to the receptor called gamma-aminobutyric acid (GABA) in the central nervous system (brain). Benzodiazepines are classified as short-acting, intermediate-acting and long-acting types.

Diazepam is a type of long-acting benzodiazepine. It is converted to nordiazepam after its metabolism in the body. Diazepam and its metabolite, which are highly lipophilic, can rapidly cross the blood-brain barrier and exert their effects. While the drug takes effect within 1-3 minutes of intravenous (intravenous) ingestion, the initiation of oral dose varies between 15-60 minutes (31). Nordazepam

is a type of benzodiazepam that is a 1,4-benzoazepine derivative. Nordazepam, nordiazepam, deoxydemoxepam or desmethyldiazepam are different names for the same molecule. The nordezapam molecule is formed as a result of the metabolism of diazepam, chlordiazepoxide, clorazepate, prezepam, pinazepam and medazepam. It acts by binding to GABA-A receptors. The half-life of nordazepam can vary between 36-200 hours due to age and gender, and it continues to interact with GABA-A receptors (32).

Chlorazepate, prezepam and pinazepam are not included in the list of benzodiazepines routinely examined in the annex of the chemical examination report. The nordiazepam detected in the blood of the concrete case, any of these 3 molecules or the result of the use of diazepam may have been positive in the body. However, nordiazepam detected in our report may have been due to the use of both diazepam and 3 other benzodiazepam derivatives. Since the level of these 3 benzodiazepine derivatives is not included in the list attached to the report, it cannot be said clearly which benzodiazepine derivative was used in this case.

γ-Aminobutyric acid-A (GABA-A) is an important inhibitory intermediate molecule in the central nervous system of humans. This molecular pathway is an area where benzodiazepines and barbiturate-derived drugs are effective. In behavioral studies, it has been determined that the use of a drug called GABA mimetic (stimulating this pathway) may adversely affect motor (voluntary movement) behaviors on the body muscles.

It is known that the inhibition of benzodiazepine metabolism by ethyl alcohol results from the inhibition of the formation of a benzodiazepine-enzyme complex with P450 (33). Because both ADH and CYP2E1 are involved in ethanol metabolism at high ethanol concentrations, the metabolism of benzodiazepines is competitively inhibited following a significant alcohol intake. On the other hand, in case of low ethanol concentrations in alcohol in social drinkers, CYP2E1 is minimally involved in ethanol metabolism and induction is not a factor. However, the mechanism governing the interaction involving both is complex (34).

Benzodiazepines, which have various clinical uses, are often used in the treatment of convulsions (episodic seizures), anxiety disorder (anxiety disorder) and muscle spasms (muscle spasms). In other words, diazepam and therefore its active ingredient nordiazepam have muscle relaxant effects. The recommended dose of the companies producing this drug, which can relax the muscle, is 5-15 mg/day. This is possible even if the dose of nordiazepam detected in the blood of the concrete case is 14 ng/ml, it is unlikely to interact with alcohol and develop a suppressive effect on the central nervous system (brain) tissue.

3. Conclusion

As a result, a narcotic drug was detected in the blood of this case, and it cannot be understood according to the content of the present report whether the body tissues have taken another narcotic-stimulant drug that is not on the routine chemical examination list. At current doses, benzodiazepine overdose poisoning cannot be mentioned as the cause of death of the case. However, if the amount of alcohol detected in the blood of the person was taken orally, the person may have lost his voluntary movements due to a temporary

suppression in brain functions due to the additive (combined) effect of alcohol and benzodiazepines. This situation is open to interpretation and due to ethical issues; human studies on interactions at these doses in the medical field are not available in the literature.

4. Conflict of Interest

There is no conflict of interest.

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