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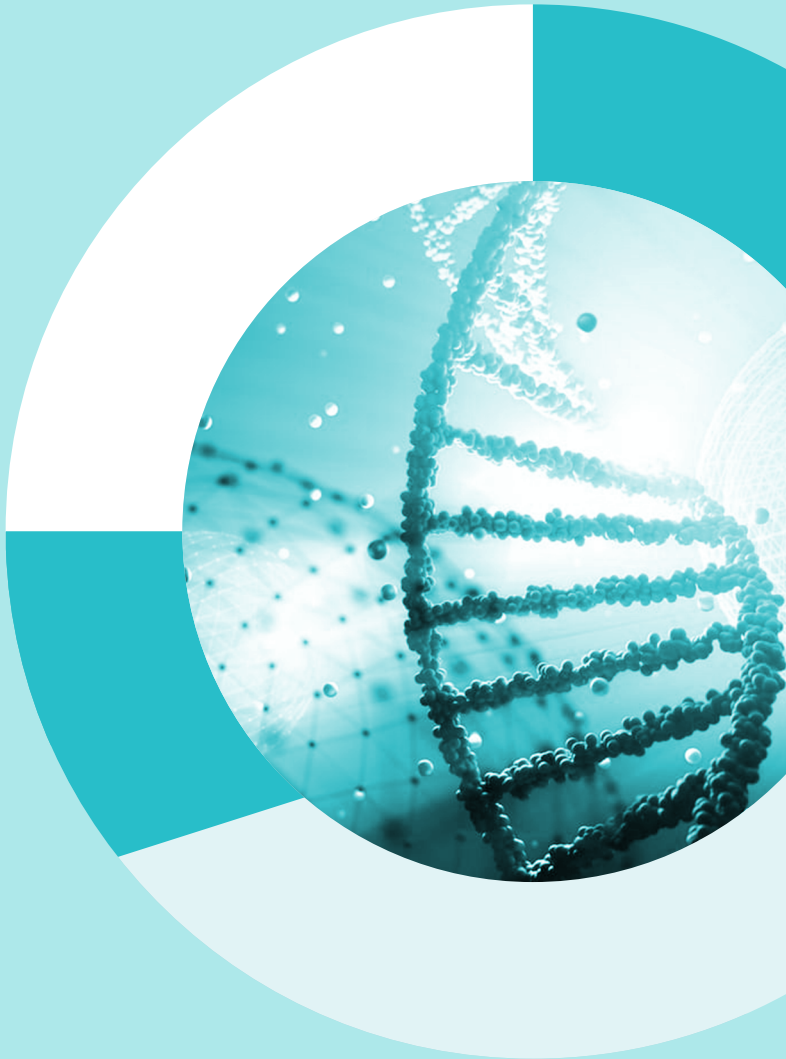
REVIEWS

ORIGINAL ARTICLES



Official Journal of Cyprus Turkish Medical Association

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AIMS AND SCOPE

Cyprus Journal of Medical Sciences (Cyprus J Med Sci), the official organ of Cyprus Turkish Medical Association.

This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

The aim of the journal is to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case report and letters to the editors.

The target audience of the journal includes healthcare professionals physicians, and researchers who are interested or working in in all fields of medicine.

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Keywords: Each submission must be accompanied by a minimum of three to a maximum of five keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database. (https://www.nlm.nih.gov/mesh/MBrowser.html).

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Cyprus Journal of Medical Sciences adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

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- Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.
- For further details, please check ICMJE Clinical Trial Policy at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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As of 1 January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual deidentified participant data will be shared

- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Cyprus Journal of Medical Sciences;

- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be

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provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The subheadings of the review articles should be planned by the authors. However, each review article should include an "Introduction" and a "Conclusion" section. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Both in-text citations and the references must be prepared according to the Vancouver style.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

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manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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Viral Nano-Bio-Sensing and SARS-CoV-2: A Literature Review

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Abstract

As new advancements and technologies are emerging in this world, so is the spread of new diseases. The world, as we know it, is moving very fast. With this pace, diseases are also borne. The spread of new viruses, such as coronavirus disease-2019, require new technologies faster and more precise than ever before. Countries all around the world are connected, and moving from place to place has become easy. For that reason, pandemics are an increasing threat. A disease is considered a pandemic when it has spread through a large area, possibly worldwide and has become an international threat. In order to limit the spread of diseases, or viruses in particular, the early detection and diagnosis of patients is essential to decrease the number of infections. Biosensors play an important role in the medical field, such as in viral detection. Nanotechnology has gained a lot of interest in its use in bio-sensing. Nano-biosensors have shown more advanced properties than regular biosensors and thus are able to detect diseases faster and more precisely than before. Our main focus in this literature review is to explore new technologies and advancements made with nanotechnology and bio-sensing in viral detection, especially in the detection of severe acute respiratory syndrome-coronavirus-2.

Keywords: COVID-19, pandemic, virus, bio-sensor, nanotechnology, nano-biosensors, SARS-CoV-2

INTRODUCTION

Coronavirus disease-2019 (COVID-19), also known as COVID-19, is an illness caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). COVID-19 was declared a global pandemic by the World Health Organization (WHO) on March 11th, 2020.[1] Back in 2003, a similar outbreak occurred, known as SARS, which was caused by the SARS-CoV infecting over 8,000 people and killing 774.[2] Coronaviruses are enveloped viruses which have S-proteins making them appear as crowns, thus leading to the name "corona" (Latin for crown). All CoV have a single stranded RNA genome. As many errors occur during RNA replication, CoV have a high mutation rate. The RNA genome encodes many structural proteins. From these proteins, the S-glycoprotein found on the surface of CoV binds to the receptor angiotensin-converting enzyme 2 (ACE2) found on the lower respiratory tract of human cells. SARS-CoV-2 uses the ACE2 receptor to infect humans.[3,4] Infectious diseases can arise due to many factors, some being the lifestyle of humans, their eating habits or their interaction with animals, as well as urbanization which allows the fast spread of diseases. Other causes include climate change which allows a disease to move to a different environment infecting more of the population, or mosquito borne diseases which move to many different areas. Furthermore, the mass production of animals during an outbreak readily spreads the disease further. Infectious diseases have spread causing epidemics and then pandemics all through history.[5]

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A biosensor is an analytical instrument which is used to accurately determine analytes in a living sample. This device is precise, delicate and has a particular measurement configuration. Since it is used for the detection of living samples, it consists of living elements such as microorganisms, organelles, cell receptors, enzymes, or nucleic acids. Due to the interaction with the sample, a signal is generated which can be electric, optical or thermal. Those signals are then transformed using a transducer to a parameter which can be measured. Figure 1 represents the different components of a biosensor.[6]

Nano-biosensors are bio-sensors which are based on the presence of nanomaterials. As the size of a material decreases, the surface area to volume ratio increases, which corresponds to a better signaling and transduction process and a better detection system.[7] The most promising nanomaterials in nano-bio-sensing include carbon nanotubes (CNTs), gold nanoparticles (GNPs), quantum dots (QDs) and magnetic nanoparticles (MNPs). These nanomaterials may be used in the transduction or bio-recognition process due to having smaller sizes, higher speeds, and faster electron transfer due to smaller distances, large surface area, using less power and lower voltages. Metallic nanostructures such as QDs (0D), CNTs (1D) and graphene sheets (2D) have been found to increase electronic properties such as when used as electrode components to improve transduction. CNTs are used in electrochemical sensing for various analytes such as in glucose, fructose, galactose, insulin, cancer biomarkers, cells and DNA. Graphene has been used in electrochemical biosensors as well as impedance, fluorescence and electrochemiluminescence biosensors to detect various analytes such as glucose, cholesterol and uric acid. QDs have excellent optical properties and various emission wavelengths based on their size and thus are used as fluorophores in optical biosensors to detect ions and various pharmaceutical analytes. They are also being used for the *in vivo* detection of cancer. GNPs have mainly been focused on usage in bio-sensing, drug delivery, cancer therapy etc. GNPs are non-toxic, biocompatible and have an inert core. MNPs have also been used in bio-sensing for the detection of various analytes such as proteins, enzymes, mRNA, DNA and tumor cells.[8]

The aim of our literature review was to discover basic virology, then explore nano-bio-sensing of different viruses, focusing on the applications of GNPs as they are the most frequently used NPs in viral detection, and then to include a summary of other NPs which are used as well. We then aimed to concentrate on COVID-19 detection as well as the current progress of nanotechnology in COVID-19 vaccines.

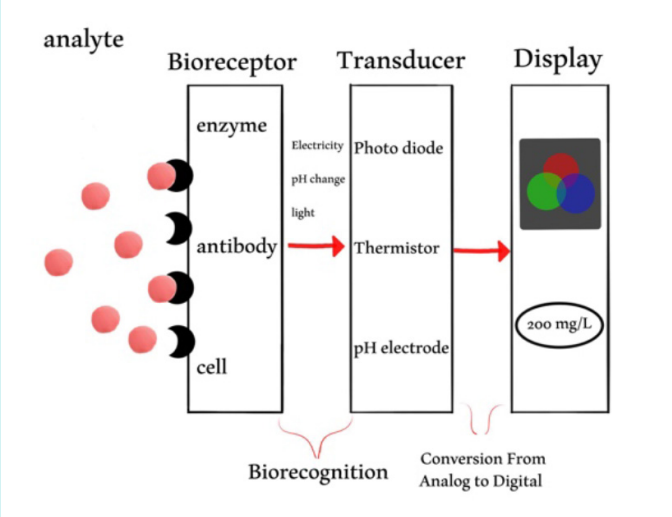

Figure 1. A schematic representation of a biosensor.

Viruses

Viruses are microscopic, subcellular entities which cannot replicate outside of a host cell. In the simplest viruses, a simple virus (virion) has just one kind of nucleic acid (RNA or DNA) and a protective protein coat. The nucleic acid carries the genetic information required to instruct the host cell's synthetic machinery for viral replication. The protein coat has two purposes: First, it shields the nucleic acid from extracellular environmental insults such as nucleases; and second, it allows the virion to adhere to the host cell's membrane, the negative charge of which would reject a naked nucleic acid.[9]

Antigens are responsible for initiating an immune response in the host cell to inhibit further viral replication and kill infected host cells. Inhibiting further viral replication is done when the body is signaled by the antigens to produce antibodies to prevent the virus from entering cells and further replicating. Infected cells are killed by cytotoxic T-cells when activated by the viral antigens. Viruses that have more than one kind of antigens (having variant antigens) are more likely to attack the host cell since an antibody for a certain serotype will not protect against another serotype.

Some viruses have a viral envelope made up of a lipid bi-layer that carry the capsid as well as the genome. Other virus may lack this envelope. The viral envelope is a lipoprotein membrane which contains protein which is virus specific and which attaches to certain receptors of certain host cells. In addition to the viral envelope, the human cell is also made up of a lipid bi-layer, therefore, it is easy for the virus to fuse into the cell and release genetic material into the host cell. The envelope, therefore, aids in the attachment to host cells. However, the envelope increases the virus' sensitivity to parameters such as heat, dryness, detergents and solvents such as alcohol. It has been clinically shown that almost all viruses which are transmitted via the fecal-oral route lack an envelope and are capable of enduring certain environments more.[10-12]

Applications of Gold Nanoparticles (AuNPs) in Virus Detection

Nanoparticles have made nanoscale bio-targets such as proteins, lipids, and viruses detectable. The size scale of nanoparticles corresponds to the size scale of biological objects, which are of importance in many medical and bioengineering applications. Despite the fact that the scales are similar, the detection of binding events at the nanoscale only results in minor perturbations on resonance, resulting in less detectable signals. This is especially problematic when it comes to identifying viruses, which might be quite infrequent in solutions. As a result, other ways for enhancing and amplifying resonance disturbances and allowing greater shifts which are observable and quantifiable are urgently needed to progress this discipline.

AuNPs have been the most frequently used NPs in the detection of viruses. A mechanism known as "size and distance dependent nanoparticle surface energy transfer" was used to detect the presence of RNA of hepatitis C virus (HCV). In this mechanism, firstly, a single strand RNA is labelled with fluorophores and absorbed on the surface of AuNPs, such that when the complementary RNA is detected, they bind together forming a double strand RNA complex (dsRNA) by a process

known as hybridization. When dsRNA is formed and released in the solution, fluorescence emission takes place. The use of AuNPs in this mechanism is as a colorimetric signal indicating the presence of the RNA of HCV by the aggregation of AuNPs which results in a color change from red to blue. It is also important to note that fluorescence intensity is directly related to the concentration of the target RNA present in the solution.[13]

Another method which is used to detect avian influenza virus (AIV) is based on AuNPs and MNPs. MNPs are combined with "AIV-specific penta-body (pVHH3B)" to detect AIV. AuNPs are labelled with "anti-AIV monoclonal antibody (mAb3C8) forming AuNPs-mAb3C8". This configuration of AuNPs is used as a detector. In this method, when the target is present, the pVHH3B reinforce the AIV on the MNPs, and then the AuNPs-mAb3C8 bind to the MNPs forming a complex. AuNPs present in this complex stimulate the oxidation of hydroquinone to quinone. Finally, the optical density of quinone is measured. This density is used to determine the amount of AIV in the sample. In other words, this density measures the amount of yellow color produced, which is directly related to the concentration of AIV present in the sample.[14]

Moreover, a system known as "fluorescence resonance energy transfer (FRET) system" was used for the detection of the DNA of the hepatitis B virus (HBV). The general concept of this system is that an atom in the higher energy state transfers its electrons to the closest atoms in a non-radiative way.[15] In this study,[6] the FRET system is composed of gold nano-rods (AuNRs) and fluorescein (FAM). Firstly, the AuNR's surface is covered with cetyl-trimethylammonium bromide (CTAB). The CTAB is used to generate positive charges on the nano-rods. Then, a single strand DNA (ssDNA) labelled with FAM forming FAM-ssDNA was added to the AuNRs solution. FAM-ssDNA was adsorbed onto the surface of the positive charges of the AuNRs and formed a ternary complex (FAM-ssDNA-CTAB-AuNRs). This configuration resulted in the FRET process to take place from FAM to AuNRs. The fluorescence intensity of FAM was reduced. The fluorescence intensity further decreased when the complementary target DNA was added to the ternary solution. This is because of an increased FRET efficiency.

The surface enhanced Raman scattering (SERS) method is used to detect the rift valley fever virus antigen based on AuNPs. Firstly, AuNPs and MNPs are combined with a polyclonal Ab specific for the target virus antigen, forming AuNPs-Ab and MNPs-Ab, respectively. The polyclonal Ab is a group of antibodies from different cells which determine various epitopes on the same antigen. Then, when the specific antigen is held by the AuNPs-Ab and MNPs-Ab, they form a three-component immunocomplex. A laser beam is then directed towards this complex and excites it. The presence of the target antigen yields a reduction in the intensity of Raman spectrum peaks, thereby providing an estimation of its concentration. This method resulted in direct and fast detection of the virus with prominent sensitivity down to 5 fg/mL even in complex samples which is achieved by magnetic particles supporting the application.[16]

In another study, a three-dimensional plasmonic nanocomposite was established, creating a SERS detector chip for the detection of several viruses and bacteria.

In this study, the hydrothermal technique was used to allow Zinc nano-rods (ZnONRs) to grow vertically on a cellulose paper containing pores (C). Then, successive ionic layer adsorption and reaction technique is used to enhance AuNPs on the ZnONR/C, forming the three-dimensional plasmonic nanocomposite. As a result of this nanocomposite, the Raman signal showed improvement and highly specific detection.[17]

For the detection of the influenza A virus, a mixture of H3N2 IAV (antigen) with AuNPs-monoclonal anti-HA antibody (AuNPs-mAb) is added to phosphate-buffered saline. The mixture is prepared with various dilutions of H3N2 IAV added to a five-fold concentrated mAb-AuNP suspension (a diluted 1/5" ratio meaning that the ratio of H3N2 IAV to mAb-AuNP is 1:5). It then undergoes incubation at 37 °C for 30 mins. As a result, H3N2 IAV can be seen by the naked eye and a color change from red to blue of the mixture is observed, this is shown in Figure 2. Finally, in order to be able to determine the concentration of the virus, a UV-vis spectrophotometer can be used. This method is not only low cost, simple and convenient, but also it is a single step detection method, accurate and specific. In addition, it does not require further amplification.[18]

In another study found in the literature, a layered complex was established creating a colorimetric medium to detect the influenza A virus (H3N2). In that study, the color change is related to the amount of hydrogen peroxide produced. First, aptamer-functionalized magnetic microparticles are needed to encapsulate the virus. Additionally, AuNPs were modified by glucose oxidase (GOx) and concanavalin A (ConA) forming a ConA-GOx-AuNPs solution which was conjugated with H3N2 virus resulting in a reaction producing hydrogen peroxide and changing the AuNPs color.[19]

In another study, an electrochemical method was used for the detection of the human immunodeficiency virus-1 (HIV-1). This method[20] is based on the direct identification of electron transfer signals from the virus. Using this method, an electrode made from indium tin oxide and coated with glass was used and AuNPs were electrodeposited on it. This configuration resulted in an improved transfer of electrons and a higher background charging current. On this modified electrode, using the self-assembly method, small pieces of antibodies were immobilized with gold-thiol bonding and various concentrations of HIV-1 virus-like particles (VLP). The VLP of HIV was successfully detected with a detection limit of 600 fg/mL-1 to 375 pg/mL-1. A summary of AuNPs in the detection of different viruses is shown in Table 1.

Other Nanomaterials Used in Viral Detection

Apart from gold NPs which are the most frequently used nanoparticles in viral detection, other nanomaterials are summarized in their viral

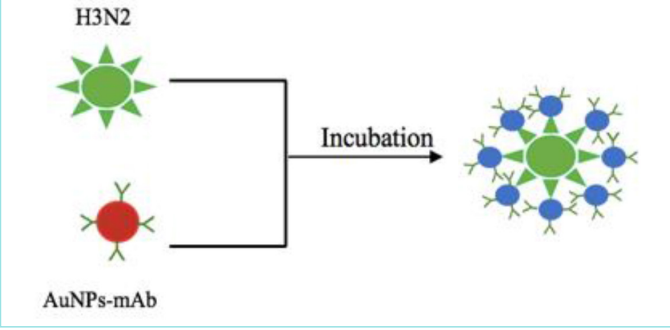

Figure 2. Method of influenza A virus detection.

Table 1. Gold NPs in the detection of different viruses

Detected	Technique	Detection limit/sensitivity down to	References
RNA of hepatitis C	AuNPs-based assay	-	13
Avian influenza	Nanoparticle-based assay	10 ng mL^{-1}	14
DNA of hepatitis B	FRET-based assay	15 pmol L^{-1}	6,15
Antigen of RVFV	Nanoparticle-based immunoassay with surface Raman scattering	Sensitivity down to 5 fg/mL	16
Several viruses and bacteria		-	17
Influenza A	Nanoparticle-based colorimetric assay	7.8 HA $1.1x10^7$ pg mL^{-1}	18 19
VLP of HIV	Electrochemical assay	600 fg/mL^{-1} to 375 pg/mL^{-1}	20

NPs: nanoparticles, AuNPs: applications of gold nanoparticles, FRET: fluorescence resonance energy transfer, RVFV: Rift Valley Fever virus, VLP: virus-like particles, HIV: human immunodeficiency virus-1.

applications. For example, a method known as cathodic stripping voltammetry used MNPs to confirm the presence of PCR-amplified DNA of the HBV.[21] An immunosensor based on CNTs was used to identify the presence of the biomarkers of the hepatitis B surface antigen. The immunosensor consists of a glassy carbon electrode, CNTs and polypyrrole propionic acid. Moreover, for the determination of HIV, a detection system based on QDs was established.[13] Also using the QDs, another system was established which is FRET-based QDs-DNA.[6] This system is used for the fast and simple identification of the DNA of HBV. In addition, a biosensor was constructed based on graphene which contains immobilized monoclonal antibodies used to detect the presence of Zika virus.[22]

In another study, a QD was embedded inside an empty shell of iron oxide, resulting in an electrochemical/fluorescence dual probe for the detection of various viruses from clinical specimens, including the hepatitis E virus (HEV), HEV-like particles, norovirus-like particles (NoV-LPs), and norovirus. Most notably, HEV-infected monkey feces were effectively identified with a sensitivity close to the gold standard real-time quantitative reverse transcription-polymerase chain reaction (RT-qPCR). This well-defined QD@MHS NPs-based nano-platform intelligently merges dual-modality sensing with magnetic bio-separation, opening the door to efficient point-of-care viral diagnostics testing[23].

Coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2)

Coronaviruses are a family of RNA viruses having large RNA genomes, infecting both animals and humans. Coronaviruses can infect both birds and mammals, and it has been shown that bats can act as hosts to the virus and pass it on to other species. Previous epidemics caused by the coronavirus have been recorded in history; this has been shown due to the viral protein mutations which cause them to bind to different cells, infecting more cells of different species. Back in late 2002, a novel deadly virus known as SARS emerged. There were 8,089 reported cases and 774 deaths with a fatality rate of 9.7%. In 2012, the middle east respiratory syndrome-coronavirus (MERS-CoV) immerged causing 2,494 reported cases and around 860 deaths in 27 countries with a high fatality rate of 34%. The new SARS-CoV-2, although less fatal, has a higher reproductive rate (R_0) of 2.5 in comparison to 2.4 and 0.69 for SARS and MERS, respectively. The reproductive rate (R_0) is a quantitative measure of the average number of transmissions from one infected person. Therefore, an R_0 greater than one means a growing epidemic. Moreover, SARS-CoV-2 has a higher incubation period (4-12 days) than SARS-CoV (2-7 days), which in turn increases its chances of transmission. The incubation period is the time of first exposure to the virus until the first symptoms start to appear.[1] Moreover, all throughout history, pandemics have wiped out populations, affected wars and societies. They have, however, also caused advancements in medicine and science. The following table (Table 2) shows several pandemics and epidemics recorded in history[24] and their estimated death tolls.

Classification of Viral Tests and COVID-19

Viral tests are based on biotechnology, specifically analyte-based bio-sensing. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) tests are necessary to decide whether a person is infected and therefore must be isolated. Since COVID-19 is generally a respiratory illness, chest X-rays, thoracic imaging and flexible bronchoscopy are also available for diagnosis and recovery. There are many drawbacks to qRT-PCR testing, such as taking from 4 hours up to 3 days to obtain results, errors in results, lengthy sample preparation and specific transportation. Moreover, the typical qRT-PCR test is inaccurate showing false results such as appearing negative to those freshly infected and positive to those who have recovered, due to it detecting dead SARS-CoV-2 in them. Therefore, alternative methods must be found to increase sensitivity and decrease time and cost.[25] Some of those alternative methods include nanofabrication and nano-science which increases effectiveness. There are 3 types of viral tests based on what they target. The first one is a genetic test targeting the viral genome. The second type is called antigenic which targets the viral proteins/antigens. Lastly, the third is called serological which targets the antibodies that are released as an immune response to a viral infection. Antigenic and serological tests are based on the antigen-antibody recognition using lateral flow assays. Antigenic tests require at least 5 days to obtain enough viral antigens to be effective and serological tests require at least 7 days for the antibodies to be produced. Antigenic test strips contain viral antibodies coated on it. Once a blood sample interacts with it, the presence of viral antigens in the blood will cause a color change due to the plasmonic resonance properties of the colloidal gold used in the strip test. Serological tests, although similar, detect the presence of antibodies instead of antigens. Those tests can detect the presence of both immunoglobulin G (IgG) and IgM which give different information on the current or past presence of the virus. After being infected with COVID-19, an immune response triggers the production of IgG and IgM in the body which fight against the virus. These antibodies

Table 2. Pandemics and Epidemics recorded in history

Disease	Year	Estimated deaths
The Athenian plague	430 B.C.	~75,000-100,000
The Antonine plague	165-180 A.D.	~5,000,000 (1/3 of the Roman population at the time)
The Justinian plague	541-750 A.D.	~50,000,000 over two centuries of recurrence
The black death	1347-1351 A.D.	~25,000,000
Spanish flu	1918-1920 A.D.	~50,000,000
HIV	1980-present A.D.	32,000,000
SARS (SARS-CoV)	2003 A.D.	774
"Swine Flu" or H1N1/09	2009 A.D.	~150,000
MERS	2012 A.D.	860
Ebola	2014-2016 A.D.	~11,315
Zika	2015-2016 A.D.	~18
COVID-19 (SARS-CoV-2)	2019-present A.D.	5,905,481 (As of: February 20th, 2022, 22:55 GMT)

HIV: human immunodeficiency virus-1, SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2, MERS: middle east respiratory syndrome, COVID-19: coronavirus disease-2019.

can be found in the blood. IgM are the first viral antibodies produced to protect you and the IgG antibodies remain in your blood shortly after recovery to insure future immunity. Improving the sensitivity and accuracy of immunoassays has been of importance recently and it has been tackled using dyes or nanoparticles which strengthen the antibody-antigen binding signal. Various nano-materials have also been used as conjugates to the bio-receptors including carbon nanoparticles, ODs, colloidal GNPs as well as liposomes and enzymes.[26]

Point-of-Care Biosensors

Point-of-care biosensors are those which can be used simultaneously while treating the patient and are at a close proximity with the patient thus providing immediate care. In poorer areas, typical testing may not be present and therefore a cheaper and easier point of care (POC) alternative was developed. Generally, there are two types of POC biosensors capable of detecting SARS-CoV-2. Those two tests are nucleic acid and antibody tests. Nucleic acid tests show early results even before symptoms appear by taking a sample from the saliva and/or mucus since the ACE2 enzyme is found in the lower respiratory tract where the sample is taken from. The antibody (IgG/IgM) test, however, is typically used when symptoms start to show or to confirm past diagnoses for the coronavirus. Being positive for IgG implies you have been infected with COVID-19 in the near past or are still currently infected. POC biosensors which can potentially be used to detect COVID-19 are chip-based, paper-based or other materials-based biosensors. Paper-based biosensors have become more commonly used than chip-based biosensors to detect COVID-19 due to their ease of fabrication and modification. Paper-based biosensors consist of a lateral flow test paper strip for the detection of IgM and IgG antibodies. The strip contains various pads including those with COVID-19 antigens conjugated with GNPs. Upon the presence of IgM and/or IgG antibodies, they react with the gold-COVID-19 antigen complex and form a reaction continuing along the strip.[27] A team of Korean scientists detected COVID-19 using a graphene-based biosensor. Field effect transistors (FET) use an electric field to control current flow. Using FET-based biosensors allows for instant and accurate sensing using small amounts of analytes without prior preparation. The assembly of a graphene-based FET was functionalized via the SARS-CoV-2 antibody on the surface for the detection of the viral spike protein. The sensor was able to detect the viral antigen via cultured COVID-19 viruses, patient nasopharyngeal swabs as well as SARS-CoV-2 virus lab samples and could also distinguish the viral protein from that of MERS-CoV. Graphene-based FET biosensors allow optimal sensing providing accurate results. The team used nanotechnology-based techniques such as the wet transfer method to deposit graphene onto a silica substrate followed by creating channels on the graphene layer via photolithography and etching which formed linearly ordered graphene on the substrate. Then, metal electrodes were added using thin film deposition. Finally, graphene was used to bridge the source and drain electrodes. The SARS-CoV-2 antibody on the surface of the graphene was immobilized via 1-pyrenebutyric acid N-hydroxysuccinimide ester by forming a chemical bond. Graphene was used as a COVID-19 transistor responding to the viral spike proteins, changing its electrical conductivity and, as a result, changing the amount of current flow and showing a response signal.[28]

Information on more than 240 Emergency Use Authorization-level COVID-19 diagnostic tests are available (as of 5th September 2020), and the number of commercially produced COVID-19 molecular tests and immunoassays is almost comparable. FIND has been evaluating over 800 diagnostic assays, more than 250 of which are quick tests which produce a response in less than 30 minutes. The use of immunoassays at the POC is routinely approved as part of the COVID-19 post-restriction management plans.[29]

Nanotechnology-Based Vaccines

Nanotechnology has been involved in the production of messenger RNA (mRNA) vaccines for COVID-19. Those are the Pfizer-BioNTech and Moderna vaccines. They are mRNA vaccines, which unlike the other typical vaccines, do not contain an inactive or weakened virus. Instead, Pfizer-BioNTech and Moderna vaccines contain genetic information that code for the S-spike protein found on the surface of SARS-CoV-2, thus, triggering an immune response and antibody production which a typical vaccine would (such as in typical weakened/inactive vector vaccines). Moreover, these mRNA vaccines are modified with lipid nanoparticles in order to overcome the limitation of vaccine degradation by the enzymes present in the body. This is done by wrapping the mRNA of the vaccines with a nano-coating made from lipid nanoparticles.[30] These vaccines have been stated to cause allergic reactions in some, triggering anaphylaxis due to the compound polyethylene glycol (PEG). The outer lipid nanoparticles are "PEGylated" or chemically bonded to

PEG molecules which increase their performance and lifespan.[31] For that reason, as well as the search for more economical nanoparticles and easier storage requirements, alternatives have been investigated such as one which has been studied at Stanford University. The study carried out at Stanford University suggests the possible use of iron nanoparticles containing ferritin proteins which have the S-spike protein attached on its surface, thus initiating an immune response and developing antibodies.[32]

CONCLUSION

The merging of nano-materials with their distinct properties along with biosensors results in them being more efficient, sensitive and selective (also known as nano-biosensors) as well as introducing new and easier methods of fabrication which are not present in ordinary biosensors. Furthermore, AuNPs showed the most potential to be applied in different methods for the detection of numerous different viruses. AuNPs are biocompatible with the human body, they have distinct optical properties, good catalytic activity and their surface can easily be functionalized.

Point-of-care biosensors play a huge role in fast detection, fast diagnosis and treatment. POC biosensors are also accessible in poorer areas due to them being easier to use by the individual and cheaper than typical qRT-PCR testing. Some POC biosensors include nanofabrication and nano-based materials such as AuNPs and graphene. Moreover, nanotechnology has played an important role in increasing the sensitivity of antigenic and serological tests. Specifically, this has been achieved by the use of colloidal gold NPs to increase the antigen-antibody signal, as well as by using several NPs as conjugates to bio-receptors such as colloidal gold, carbon and ODs.

From viral detection to producing a viral vaccine, nanotechnology has shown great potential and is currently being implemented. Over 12 vaccines aimed at targeting the COVID-19 virus are already in clinical trials. From which, nanofabrication has been incorporated into mRNA lipid-based nanoparticle vaccines.[33] Moreover, a team of researchers at Steinmetz Lab in UC San Diego suggest that the production of a plant-based nanoparticle vaccine, extracted specifically from black eyed peas, will be more sustainable and easier for manufacturing at a global scale in such a growing pandemic. Additionally, a team at Stanford University suggests the possible use of an iron nanoparticle-based vaccine.

Nanofabrication is a growing field with many frequent discoveries. Public, health and economic concerns must be addressed to produce globally safe and cheap nano-based vaccines as well as obtain an effective, easily accessible nano-biosensor which can serve and benefit the public and provide a faster and more precise detection method in order to reduce the spread of infections.

MAIN POINTS

- COVID-19 is an illness caused by the SARS-CoV-2 virus which was declared a global pandemic by the WHO on March 11th, 2020.
- Nano-biosensors are biosensors based on the presence of nanomaterials which provide a better detection system.
- Nanoparticles such as AuNPs have been used to improve the antibody-antigen binding signal in viral tests based on lateral flow assays.
- Nanofabrication has been incorporated in mRNA lipid-based nanoparticle vaccines such as in the Pfizer-BioNTech and Moderna COVID-19 vaccines.

ETHICS

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.K., S.A., Design: D.K., M.M., Supervision: S.A., Ş.K., Materials: D.K., M.M., Data Collection and/or Processing: D.K., M.M., Analysis and/or Interpretation: D.K., S.A., S.B., Ş.K., Literature Search: D.K., M.M., Ş.K., Writing: D.K., Critical Review: S.A., S.B.

DISCLOSURES

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

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REVIEW

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The Development of Psychiatry in the Turkish Republic of Northern Cyprus from Past to Present

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Abstract

The Turkish Republic of Northern Cyprus (TRNC), which is located in the northern part of the island of Cyprus, has a complex history and was established with great difficulties. Like many other domains, the field of psychiatry was rebuilt after the wars in the TRNC. Hospital-based mental health services have continued in the TRNC since the first hospital was established after the war of 1974. The current mental health law was created during the period of British administration and anew draft law is now being considered in the parliament. Rates of suicide increased in the TRNC from 1992 to 2012, and domestic violence, homophobia, transphobia, and psychoactive substance abuse are also important problems. However, many institutions now carry out preventive and rehabilitative studies in the field of mental health and this is a promising and significant development. Conducting a study which determines the mental health profile of the TRNC is important for shaping future studies in the field of mental health. In addition, it is important in terms of designing initiatives to make mental health services more community-based. Creating a database for scientific studies will also contribute to a better and more systematic organization of the information. This will also help nurses receiving postgraduate education in the field of mental health and psychiatric nursing to improve the care given to individuals/patients in institutions providing mental health services. The number of nurses working in psychiatry should be increased and programs given in order to allow them to become more properly qualified.

Keywords: Cyprus, Turkish Republic of Northern Cyprus, psychiatry, psychiatric nursing

INTRODUCTION

"Awareness" is an important concept for all mental health professionals in general. With regard to specific mental health policies and practices, it is necessary that professionals are aware of what has happened in the past and the stages which have occurred up to the present day. Past, present, and future are not separate from each other. Having an awareness of past and present developments may determine the direction of future plans.

Wars are negative experiences for public mental health, but they contribute to developments and changes in the field of healthcare.[1] In 1963 and 1974, two major wars took place between Turkish Cypriots and Greek Cypriots, causing great suffering for the individuals who lived through them.[2,3] After the 1963 war, the residential areas of the Turkish Cypriots and Greek Cypriots were divided along a ceasefire line called the "green line". After the 1974 war, Cyprus was separated into a northern and a southern area, divided by a buffer zone. Turkish Cypriots began to live in the north of the island and Greek Cypriots in the south. Later, two different republics, the Turkish Republic of Northern Cyprus (TRNC) and the Republic of Cyprus were established.[1,4] Turkish Cypriots experienced many rapid changes as a result of these wars. Economic and social structures were upended, living spaces were bombed or abandoned, day-to-day social life was profoundly altered, many deaths were witnessed, and great pain and suffering were experienced. These negative changes caused deep psychological strains.[3,4] The number of suicide attempts and completed suicides increased in Northern Cyprus between 1970 and 1990. While five people attempted suicide in 1970, 34 people attempted suicide in 1990.[5] The changes that Turkish Cypriots

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experienced in the field of mental health started with the war of 1974: the island's sole psychiatric hospital remained in the south, while there was an emerging need for mental health services in the north.[2,6,7] Today, there are two mental health hospitals (one private hospital and one state hospital) in the TRNC.[8,9]

Examining specific studies on mental health in Northern Cyprus, according to the study conducted by Yağlı et al.[5] to determine suicide attempts and prevalence, five people attempted suicide in 1970 and this number increased to 34 in 1990. According to their study, there was an increase in suicide attempts and completed suicides in Northern Cyprus between 1970-1990. The study by Sönmez et al.[10] investigating the rate of suicides with drugs reported that suicides had continued increasing from 1992 until 2012. Although there is no study indicating the general mental health profile of TRNC, studies have reported that suicide rates continued to increase from 1992 to 2012,[5,10] and that psychoactive substance abuse is an increasing problem in TRNC.[11-16] In addition, problems such as domestic violence,[17-19] and homophobia and transphobia against LGBTI individuals[20] have been observed. These issues indicate there is a gradually increasing need for psychological care in the Northern Cypriot population. It is thus important to examine the mental health services being provided today and to conduct studies on how best to promote and maintain mental health.

No literature has been compiled about psychiatry in the TRNC. When history is not written, it disappears from view over time. Knowing about and understanding the developments in the field of psychiatry from the past to the present is important in helping to develop policies for the future. To this end, this study aimed to explain the history of psychiatry in Northern Cyprus, and this study may provide a basis for new studies in the field of mental health.

CYPRUS

In order to better understand the issue of psychiatry in Northern Cyprus, it is important to first examine the features of the island. Cyprus is located in the eastern Mediterranean and is the third-largest island in this region. It consists of two different states, the TRNC and the Republic of Cyprus. Due to its geographical location, the island of Cyprus has historically been able to control trade routes through the Eastern Mediterranean and to and from the Middle East. For this reason, many civilizations have tried to establish sovereignty over Cyprus, which has led to it being the focal point of many international conflicts.[21,22]

Cyprus was part of the Ottoman Empire between 1571 and 1878. During this period, Turks and Greeks lived on the island together. In 1878, in exchange for various promises, Cyprus was leased to the British Empire and placed under the administration of the United Kingdom. Under the Treaty of Lausanne, the free migration of Turks was allowed, and many Turks emigrated. During this period, the population of Turkish Cypriots decreased compared to Greek Cypriots due to emigration.[21] In a decree of 1917, those people living on the island were asked to become British citizens within two years. A large number of Turks, who did not accept this decree, emigrated from Cyprus to various parts of Anatolia. The United Kingdom proclaimed Cyprus a "Crown Colony" of the British Empire in 1925.[4,23] Between 1955 and 1959, the *Ethniki Organosis Kyprion Agoniston* (EOKA) (in English: the National Organization of Cypriot Fighters), established by Greek Cypriots and led by George Grivas, demanded "*enosis*" (the union of the island with Greece). Turkish Cypriots, on the other hand, established the Turkish Resistance Organization. Turkish and Greek leaders reached a consensus and established the Republic of Cyprus in 1959. However, this republic could not bring peace and harmony to the island. In 1963 internal conflicts degenerated into fully-fledged armed fighting between the two communities on the island. The loss of life in this war caused great suffering. After the war, a ceasefire line known as the "Green Line" was established. Henceforth, Turks and Greeks lived in different areas. In 1974, the EOKA leader Nikos Sampson carried out a military coup with the support of the Greek National Guard Forces to overthrow President Makarios and to declare a Greek Republic in Cyprus.[4] At the same time, attacks against Turks began on the island. The 1960 Treaty of Guarantee allowed Greece, Turkey, and the United Kingdom to unilaterally intervene to restore democracy in Cyprus in the event of a coup if attempts to garner multilateral support failed. On the basis of Article 4 of the Treaty of Guarantee, Turkey carried out two peace-keeping military operations (Operation Peace) to counter the EOKA in 1974. The first Operation Peace was implemented on July 20th, 1974. Turkish troops took control of Kyrenia on July 22nd and stopped advancing after a ceasefire. Meanwhile, Nikos Sampson's leadership ended and he was replaced by Klerides. The three guarantor powers, Britain, Greece, and Turkey, as required by the treaty, met for discussions in Geneva between the 25th July and 30th July.

At the 1st Geneva Conference, Operation Peace was found to be legitimate under Article 4 of the Treaty of Guarantee. Turkish administration of some of the island and the presence of the Turkish Armed Forces were accepted. As a result of the conference, a protocol was signed in which two different administrations were accepted, Turkish and Greek. It was decided that the security of mixed villages would be protected by a United Nations Peacekeeping Force. However, the implementation of these decisions was not successful.

Turkey conducted a second operation on August 14th, 1974. Since then, the northern part of the island has been under the control of Turkish Cypriots. As a result of these operations, aimed at maintaining peace and stability on the island, many Turkish Cypriots were saved and a stable, peaceful environment was established. The efforts to connect Cyprus to Greece, which had carried on for many years, were prevented. The "Green Line" borders were determined after the second Operation Peace, and Turkish Cypriots gathered in the north of the island, and Greek Cypriots in the south. The TRNC was established in 1983. The Greek Cypriot administration in the south of Cyprus established the Republic of Cyprus in 2004. This republic became a member of the European Union as the official and legitimate state of the island.[24,25]

Psychiatry in Cyprus

Treatment relating to mental illness in Cyprus began with the establishment of sanatoriums in the Ottoman Period.[21,26] In this period, the treatment of mental illness was the domain of mystics and shaman-like figures.[27] During the Ottoman rule, these sanatoriums became highly developed institutions in terms of the therapeutic practices used compared to other places in the world. Islamic communities were generally tolerant of individuals with mental health problems, and treatments included the use of music. Individual patients were not isolated from society and an attempt was made to treat them humanely.[28-30]

With the leasing of Cyprus to the British Empire, the period of British administration began.[21] The Mental Illness Law enacted during the

British rule provides information about that period. Individuals with deteriorating mental health were hospitalized in a hospital known as the "madhouse", located near Nicosia. Although there was training in the field of mental health for nurses in England in the 1940s,[2,6] nurses were not specifically mentioned in the law.[31] Before 1974, there was a 653-bed hospital, known as the "Mental Hospital", serving all of Cyprus during this period. In the Mental Hospital, activities such as basket-weaving were conducted for therapeutic purposes. Patients who were able to work were paid a little. However, no emphasis was placed on the privacy of the hospitalized patients, and there was no distinction in terms of room accommodation according to the type of patient.[7]

With the wars, the lifestyle of Turkish Cypriots changed, and many areas, including mental health, needed to be rebuilt. Living spaces were bombed, there was extensive loss of life, families were torn apart and suffered great losses, and economic structures and day-to-day social life changed. After all these changes, it was inevitable that mental difficulties would be experienced.[3,4] A study conducted by Yağlı et al.[5] to determine suicide attempts and prevalence in 1992 found that five people had attempted suicide in 1970 and this number increased to 34 in 1990. Also, their study determined that suicide rates were at a minimum in 1974 and at a maximum in 1985 and were encountered more frequently in women than men. However, completed suicides were more common among men. These results show that there was an increase in suicide attempts and completed suicides in Northern Cyprus between 1970 and 1990.[5] Although the need for mental health services in Northern Cyprus increased after 1974, the only hospital remained in the southern part of the island. Thus, an effort began to establish a hospital in Northern Cyprus and re-establish psychiatric health care.[2]

Development of Psychiatry in Northern Cyprus

The mental health field in the north of Cyprus was born from a huge gap and profound need. After the war of 1974, the island was divided and in a state of disorder. The Mental Hospital that had previously served both Turks and Greeks remained in Southern Cyprus, and there was no hospital in the north capable of meeting its mental health needs.[2] The first stage in establishing mental health services in the TRNC thus began. Married couple Baykal and Hüseyin Sarper, who were the first qualified Turkish psychiatric nurses in Cyprus, had trained in Psychiatric Nursing in England in 1947. After completing their education, they started working at the Mental Hospital. Baykal Sarper was the nurse in charge of the women's ward, while Hüseyin Sarper was the nurse in charge of the men's ward. They worked with the Greek doctor, Migelidis, the chief physician of the hospital.[2,6] During the 1974 war, the Sarpers, in cooperation with Turkish psychiatrist Dr. Sezai Sezgin, converted the Victoria Girls High School into a mental health clinic,[2] later known as the Nicosia Mental Health and Neurological Diseases Hospital.[32] Mentally ill individuals were provided with care in this clinic during the war,[2] and a total of 77 individuals (52 soldiers, 20 mujahedeen, and five civilians) were hospitalized in this clinic during the 1974 conflict.[32] As a result of the fighting, the Turkish patients hospitalized in the southern part of the island could not leave the hospital, and although the psychiatric nurses wanted to transfer these individuals to the Turkish region, they were unable to do so. However, various activities, such as a volleyball tournament, were conducted in the mental health clinic to reduce the trauma caused by the war.[2]

During the course of the 1970s, in various conferences and meetings attended by physicians, it was stated that relations with other medical fields should be maintained, that the Open Door method should be used and that individuals should be treated in the community where possible to make them less isolated from society at large. Polyclinic services relating to mental health were provided in the Famagusta region in Cyprus, while those individuals being treated at the Nicosia Mental Health and Neurological Diseases Hospital were treated with menstrual training, occupational therapy, ECT, electro-chemical shock therapy, Galvano-Faradi therapy, and tranquilizers.[32] An additional mental health clinic was subsequently established in the former Selimiye Primary School. This building had three male wards, four single-patient rooms, a kitchen, dining hall, occupational therapy workshop, as well as an administrative section with a polyclinic. On the 25th June, 1981, a new hospital, the Barış Mental and Neurological Diseases Hospital, came into service. This hospital still provides service as a state hospital, and polyclinic services are provided in many regions. The Barış Mental and Neurological Diseases Hospital has a capacity of 180 beds. However, no information is available on the numbers of specialized mental health and psychiatric nurses in the hospital at its founding.[8]

Even today, the number of institutions providing inpatient psychiatric services in North Cyprus is very limited. "Pembe Köşk" was the first addiction and rehabilitation center in the TRNC, operating between 2002 and 2010. After a nine-year break, it reopened in 2019 and now serves as the first private psychiatric hospital in the TRNC.[33] Therefore, there are now two in-patient psychiatric hospitals in the TRNC, one private and one public-sector hospital. In addition, polyclinic services are provided in a number of private hospitals, state hospitals, and health centers.

In terms of psychiatric education, The Mental Health Institute was established in 2005. This institute provides certificated programs in "psychoactive substance addiction counseling" for mental health professionals. Several other educational programs are also provided within the institute, including training in psychodrama, sports psychology, clinical therapy interview techniques, forensic psychology, child attention tests, life skills, management skills, body language, and motivational interview techniques.[34]

The current law regarding mental health in Northern Cyprus was established during the period of British rule in 1931 as the "Mental Illness Law".[31] Studies are currently underway with the aim of passing a new law. On the 25th September, 2018, the draft Mental Health Law was submitted to the parliament.[35] As of the time of writing, there is no study investigating the mental health profile of the Northern Cyprus society. However, a study conducted to determine suicides with drugs in Northern Cyprus between 2002-2012 found the mean age of women attempting suicide to be 25.80±11.36 years and the mean age of men to be 27.94±12.44 years. Also, that study found that suicide attempts were encountered most in spring at a rate of 27.6% and least in winter at a rate of 20.4%. Examining suicide attempts in terms of the year; 158 people attempted suicide in 2002, 223 people in 2004, 193 people in 2005, 251 people in 2006, 231 people in 2007, 208 people in 2008, 238 people in 2009, 237 people in 2010, 216 people in 2011 and 196 people in 2012.[10]

A study conducted by Çakıcı et al.[15] investigating the prevalence of drug abuse in the TRNC found the rate of illegal drug abuse to be 3.0%. Another study conducted by Çakıcı et al.[13] in 2008 found that this rate had increased to 7.7%. Another study determined that the lifelong rate of smoking among primary school students was 10% in female students,

11.8% in male students and the lifelong rate of drinking alcohol among primary school students overall was 23.5%.[11] In addition, the rate of illegal drug abuse among high school students increased from 2% in 1996 to 5.2% in 2015. Also, the rate of taking tranquilizers, which are classified as other psychoactive substances, was 3.2% and the rate of taking volatile substances was 2.9%. When examining the reasons for taking other psychoactive substances, high school students took these substances mainly for soothing their nervousness (13%) and secondly for relaxing (6.5%).[16] In Northern Cyprus, psychoactive substance abuse has become an important problem from primary school until adulthood.

In a study conducted on the levels of aggression in children, 5th-grade students in primary school were found to be moderately aggressive.[36] This shows that violent behavior in the TRNC begins in childhood. Violence against LGBTI individuals is also common. Under the aegis of the "Unspoken Project", a two-stage study of homophobia and transphobia in the TRNC population was conducted, and violence against LGBTI individuals was found in the results of the first stage. As a result of this, attempts were made to increase societal awareness of these issues, and a second study was conducted. However, in the second study, it was observed that homophobia and transphobia had continued.[20]

A study conducted by Masaroğulları and Uzunboylu[19] to investigate the reasons of violence against women found that the province with the highest rate of violence was Gazimagusa. Partner jealousy was considered the most frequent reason among violence types at a rate of 74% and women were forced into sexual intercourse by their partners at a rate of 14%. A study conducted by Mammadov[18] to examine the state of pregnant women being subjected to domestic violence in Northern Cyprus determined that 74.9% of women were subjected to economic violence, this rate increased to 76.6% during pregnancy, 48.9% were subjected to verbal violence, this rate dropped to 41.1% during pregnancy, 35.6% were subjected to emotional violence, this rate dropped to 27.9% during pregnancy, 21% were subjected to sexual violence, this rate dropped to 19.2% during pregnancy, 2.7% were subjected to physical violence and this rate dropped to 0.9% during pregnancy. In Northern Cyprus, violence against women and LGBTI individuals and psychoactive substance abuse are important problems. Interventions aimed at protecting the mental health of women and LGBTI individuals who are members of at-risk groups and the prevention of psychoactive substance abuse are considered to be important.

In considering mental health issues, the safeguarding and improvement of the mental health of healthcare professionals themselves can also be addressed. In a study conducted with 350 nurses working in a state hospital in TRNC, general symptoms of mental disorder were found in 50.3% of nurses. 65.7% experienced somatization, 57.2% experienced obsessive-compulsive symptoms, 50% experienced anxiety, 53.3% experienced hostile thoughts, 60% paranoid thoughts, and 47.2% psychotic thoughts.[37] These data are not sufficient to determine the mental health of healthcare professionals, but it is important to improve the quality of service, to protect and improve the mental health of healthcare professionals, to conduct further research, and to implement initiatives in this regard. In a study conducted on the mental state of 553 university students studying in the field of health in the TRNC, individuals from broken homes, those with less income than their expenditure, those who were in their final year of study, and those who had a family history of mental illness were found to be at risk of developing psychiatric symptoms.[38] It is important that the number of studies on the mental state of healthcare professionals during their student years be increased, and that preventive interventions be planned in this period to protect and improve the mental health of the individuals in at-risk groups. A study conducted with 560 students studying in the field of health at a private university in the TRNC found that students see individuals with mental health problems as dangerous, experience frustration and desperation in their interpersonal relationships with them, and have negative attitudes towards these individuals.[39] Healthcare professionals have an important role both in the delivery of services and in the shaping of mental health policies. Providing training to combat their negative attitudes while they are still studying may help them to change their outlooks.

In the TRNC, statistical studies are carried out by the Ministry of Health, Inpatient Treatment Institutions, and the Primary Health Services Department. According to the most recent data published by these institutions in 2018, the total number of patients in the state psychiatric hospital was 1,694, the average number of patients in one day was 57, and the total number of physicians was 13. In these published data, it was considered important to include statistics such as specific diseases, the total number of nurses, the total number of patients per nurse, the total number of psychiatrists, and the total number of patients seen per day.[40] These data suggest that mental health needs are increasing, and that the entire society, including healthcare workers, needs better and more extensive preventive and rehabilitative mental health services.

Preventive and Rehabilitative Health Services in Northern Cyprus

As in all health services, the implementation of a preventive health policy in mental health services is important. When a preventive health policy is implemented, factors which may lead to the illness are revealed and the illness can be prevented with early intervention. Some mental illnesses may continue longer, and at that point, there will be a need for the support of rehabilitation centers.

A variety of different preventive healthcare and rehabilitation services are provided in Northern Cyprus, including Social Work Centers, the Lapta Rest Home, the Nicosia Kindergarten, Counseling Support for Families, Rehabilitation Centers for Disabled People over 18, the Social Aid Unit, the Martyrs and Veterans Unit, the Women's Shelter, Family Education programs, the Kalkanlı Living House, and the Accessible Living House. With regard to domestic violence, the "Domestic Violence and Violence against Women Form" was designed as a result of the efforts of the Youth, Family Support, and Education Center (YFSEC) to create a domestic violence database in TRNC. This form was introduced to police officers and healthcare workers in 2012.[41] In addition, the "Combating Domestic Violence Coordination Mechanism" was established in 2018: the Ministry of Labor and Social Security, the Ministry of National Education and Culture, the Ministry of Health, the Turkish Municipality of Nicosia and the SOS Children's Village Association signed a protocol to work cooperatively to prevent violence against women by collecting data and providing training.[42] The Department of Gender Equality was established in December 2018. At the same time the "ALO 183" helpline was set up to report child neglect and abuse, and violence against women. Free legal aid was also provided.[43]

To combat drug abuse, an Anti-Drug Commission was established within the Prime Ministry on the 3rd September, 2014. This Commission has pioneered, planned and implemented initiatives to prevent psychoactive substance abuse. The "ALO 1191" Addiction Counseling

and Support Line, a 24-hour, seven-day-a-week helpline was opened on the 26th June, 2019. In addition, awareness-raising training is frequently conducted.[44]

In Northern Cyprus, preventive and rehabilitative studies are conducted in most areas. However, we have encountered no study regarding the effectiveness of these studies. It is believed to be important to reveal data regarding the effectiveness of studies through scientific studies and to shape future studies with the results acquired. In Turkey, studies are conducted regarding domestic violence, violence against LGBTI individuals, suicides and psychoactive substance abuse. The results of these studies are very important, but mental health needs are not limited to them. In order to provide mental health services in line with the needs of the people, it is necessary to conduct a study containing the mental health profile and to shape policies according to these needs. Shaping policies in terms of institutions and interventions protecting mental health is important in decreasing the prevalence of mental illnesses and increasing the quality of services.

CONCLUSION

Northern Cyprus has a hospital-based mental health service. Many developed countries adopt preventive health services and have community-based mental health systems.[45] When a hospital-based system is used, it tends to focus on the individual's disorder rather than the individual themselves, and especially on periods of exacerbation or crisis. The factors which lead to the disease are overlooked and untreated, more frequent periods of acute crisis may occur and social stigma may increase as a result. In addition, biopsychosocial care is not provided, and how an individual functions holistically is not focused on. Individuals may thus remain hospitalized for many years, and, when they are discharged from the hospital, they may be left to deal with their illnesses alone, leading to re-hospitalizations. These repeated hospitalizations are known as the "revolving door phenomenon". They harm the individual and increase the need for beds, personnel, and thus also give rise to increased costs.[46] In environments where the individual's ability to function is disturbed for many years, the individual cannot be healed.

The mental health profile of the TRNC can be revealed through studies, and initiatives should be designed to make mental health services more community-based. In this context, it is important to design a mental health action plan and work on a new mental health law. Since the current mental health law was created during the period of British administration, occupational groups working in the field of mental health should come together to prepare a new mental health law that will be community-based and that will decide on which service areas need to be prioritized.

Preventive and rehabilitative studies have been conducted in many fields but there are difficulties in accessing the data of some studies. It is important that the studies be followed up at regular intervals in order to be aware of and to understand any developments which may have occurred. Creating a database of these scientific studies will contribute to the systematic organization of information.

There has been no study revealing the mental health profile of the TRNC to date. Carrying out such a study is important in terms of designing future studies on mental health in the TRNC. It is essential to ensure accessibility to data, such as disease-specific statistics, the number of personnel working in mental health, the number of patients per staff member, the number of beds, etc. It is also important that activities be conducted to raise the awareness of healthcare professionals and to combat any negative attitudes towards people with mental health issues. These activities should begin while they are students and continue throughout their professional lives. Further research is also needed to determine the mental health status of healthcare professionals, and interventions for at-risk groups should begin during their period as students.

Another problem in the mental health field in the TRNC is that specialization in nursing has not yet been established. Currently, there are psychiatric nursing graduate programs at many universities in the TRNC. The contribution of the academic studies of psychiatric nurses who graduated from these programs, especially thesis research in mental health issues is important. However, the number and quality of nurses who receive postgraduate education in psychiatric nursing needs to be increased.

There are several specialist psychiatric nurses doing master's degrees; however, most of them directly provide care to psychiatric patients, carry out their duties in other clinics or work in the academic field in educational institutions. Having nurses with a postgraduate education in the field of mental health and psychiatric nursing may improve the care given to individuals in those institutions providing mental health services. Nurses working in psychiatry should be able to gain further qualifications through certificated programs.

It is important and promising that there are many organizations in the TRNC offering preventive and rehabilitative activities in the field of mental health. Psychiatric nurses can contribute their experience to institutions such as the Department of Gender Equality, the Drug Enforcement Commission, the YFSEC, and the Rehabilitation Center for Disabled People over 18.

MAIN POINTS

- There is no updated mental health law, policy text or action plan in Northern Cyprus.
- Psychoactive substance abuse, domestic violence, suicide, homophobia and transphobia are important problems.
- A hospital-based system is currently used. It is important to design initiatives to make mental health services community-based.
- Research on mental health is limited.

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REVIEW

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Quercetin: A Phytochemical with Pro-Apoptotic Effects in Colon Cancer Cells

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Abstract

The anti-carcinogenic effects of polyphenols have been demonstrated over the years. Polyphenols can show anti-carcinogenic effects by providing signal transduction related to cancerous cell growth, suppression of oncogene expression, arachidonic acid metabolism, inhibition of pro-inflammatory pathways, triggering apoptotic cell death, and inhibition of angiogenesis. The capacity of phenolic compounds due to their effects on many signaling pathways in cells might indicate the potential use of polyphenols as anti-carcinogenic agents. An important and well-studied polyphenol, quercetin, has been shown to have anti-inflammatory and anti-carcinogenic effects. Apoptosis is activated by many intracellular and extracellular signals through two main signaling pathways; the extrinsic pathway and the intrinsic pathway, and regulated by many proteins. In addition to the anti-inflammatory effect of quercetin, its anti-carcinogenic effect is a topic of interest. Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in the mitochondrial membrane potential. In addition, quercetin also induces apoptosis through the activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, caspase-9, and inhibition of anti-apoptotic proteins such as Bcl-2. In conclusion, given the pro-apoptotic and anti-cancer effects of quercetin, its potential for use as a component of cancer therapy might be suggested as an alternative to other colon cancer treatments.

Key words: Quercetin, colon cancer, polyphenols, apoptosis, anti-carcinogenic, cell death

INTRODUCTION

In recent years, foods and nutritional components with high therapeutic properties have gained importance when the side effects of drugs used in cancer treatment are considered.[1] The anti-carcinogenic effects of polyphenols have been demonstrated over the years.[1] Many polyphenols including catechin, isoflavone, lignan, flavones, ellagic acid, red wine polyphenols, resveratrol and curcumin have been shown to have anti-carcinogenic and chemo-preventive effects with different mechanisms depending on their dose.[2] Polyphenols can show anti-carcinogenic effects by providing signal transduction related to cancerous cell growth, suppression of oncogene expression, arachidonic acid metabolism, inhibition of COX-2 activity, triggering apoptotic cell death, inhibition of angiogenesis, and inhibition of the NF-kB pathway. The capacity of phenolic compounds due to their effect on many signaling pathways in cells might constitute the potential use of polyphenols as anti-carcinogenic agents. An important and well-studied polyphenol, quercetin, has been shown to have anti-inflammatory and anti-carcinogenic effects.[3]

Quercetin is a phytochemical in the flavonol group of phytochemicals commonly found in many vegetables and fruits, such as onions, apples, grapes and blueberries and they are believed to induce apoptosis.[3] Apoptosis is activated by many intracellular and extracellular signals through two main signaling pathways and is regulated by many proteins. The extrinsic pathway is characterized by the activation of death receptors

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in the cell membrane, and the intrinsic pathway is characterized by the activation of the mitochondria-apoptosome system.[4] Quercetin might exert anti-inflammatory properties by suppressing NF-kB translocation and the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β.[2] In addition to the anti-inflammatory effect of quercetin, its anti-carcinogenic effect is a topic of interest. Quercetin has the potential to exert anti-carcinogenic effects by inducing intrinsic and extrinsic apoptotic pathways and suppressing cell migration and growth. In addition, quercetin has the potential to suppress proliferation by inhibiting important signaling pathways in carcinogenesis such as MAPK, JAK-STAT, and PI3K-Akt.[5] Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in the mitochondrial membrane potential. In addition, quercetin also induces apoptosis through activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, caspase-9, and the inhibition of anti-apoptotic proteins such as Bcl-2.[6]

In this review, we aimed to examine and briefly summarize the pro-apoptotic effects of quercetin in colorectal cancer (CRC).

Development of Colorectal Cancer

CRC is the 3rd most common type of cancer in men and the 2nd most common in women. The World Health Organization reported that the incidence of CRC in men was 10.2%, and 9.5% in women.[7] Colon cancer is a disease of the large intestine which starts with the cecum and ends with the anus.[8] The intestinal wall from outside to inside consists of serosa, muscularis peopia, submucosa and mucosa.[8] Typically, CRC develops from precancerous polyps which are localized growths of abnormal cells within the intestinal mucosa. Molecular changes such as genetic and epigenetic mutations, and also histological changes may begin to accumulate within polyp cells; these changes start stepwise progressions from premalignant polyps to invasive carcinoma. In CRC, chromosomal instabilities (CIN), genetic and epigenetic mutations can create growth and proliferation advantages for cells.[9] Deficiency in the expression of tumor suppressor genes such as adenomatous polyposis coli (APC), p53, MCC, DPC-4 (pancreatic corsynomal deletion-4), and mutations in oncogenes such as RAS, Src (cytoplasmic tyrosine kinase) are genetic changes in colon cancer which contribute to colon cancer development (Figure 1).[8]

The *APC* gene is responsible for encoding-catenin, which is involved in many cellular processes such as cell adhesion, migration, signal transduction, microtubule assembly and chromosome separation.[10] The tumor suppressor capacity of the *APC* gene is related to its effect on β-catenin.[10] The Wnt/β-catenin pathway is an intracellular signaling pathway in which growth signals may be effective in tissue homeostasis and morphogenesis and are associated with the development of many cancers, including CRC as a result of its mutation.[9] In addition, the *APC* gene mutation is closely related to the development of familial adenomatous polyposis (FAP).[11] FAP is an autosomal dominant hereditary disease characterized by the development of adenoma or polyp in the colon or rectum.[12] APC mutation contributes to carcinogenesis by affecting the cell cycle and different cellular events in addition to the FAP and Wnt/β-catenin pathway.[13] Mutations in genes such as p53, p21, or pRb (retinoblastoma protein) cause a decrease in the restrictions on cell division and tumor formation. It enables the activation of the E2F transcription factor, which stimulates the synthesis of proteins required for phosphorylated pRb DNA synthesis, and the synthesis of proteins required for cell division. Cell cycle and division are regulated by cyclin-dependent kinases. pRb phosphorylation is regulated by cyclin dependent kinase-2 and cyclin E complex. As a result of DNA damage activating the *p53* gene, cyclin stimulates the synthesis of p21, which is an inhibitor of cyclin-dependent kinase-2 complex, and thus, the damaged cell cycle with DNA damage is inhibited.[14] The *p53* gene affects cancer cell apoptosis, cell cycle escape, cellular aging or DNA repair, and it is thought to be mutated in 50% of human malignancies.[15] Ras pathway activation affects the differentiation, movement, survival and proliferation of cells. The binding of epidermal growth factor to the epidermal growth factor receptor, which is its receptor, causes a series of autophosphorylation within the cell, stimulating Raf-MEK-ERK and PI3K-Akt signaling, such as Ets, Elk-1 (ETS-like protein 1), and Myc. It causes the stimulation and proliferation of transcription factors. In 90% of SRMs (SRMS Src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristoylation sites), the *Kristen rat sarcome virus (KRAS)* gene is mutated.[16]

Risk Factors for Colorectal Cancer Development

Obesity, physical inactivity, Western dietary habits, alcohol consumption, smoking, age, history of inflammatory bowel disease, family history of CRC, genetic predisposition, Lynch syndrome (hereditary non-polyposis CRC), familial adenomatous polyposis, ethnicity and type 2 diabetes are risk factors which contribute to the development of CRC.[17] It is suggested that 25% of CRC cases have familial CRC history and 5-6% of them are caused by mutations in the genes related to CRC.[18] Mutations in genes such as APC, MUTYH, MLH1, MSH2, STK11, SMAD4, BMPR1A and PTEN contribute to the development of CRC.[18] The genetic basis of CRC development is associated with two mechanisms: chromosomal and microsatellite instability.[19] Changes which affect processes such as chromosome number deletion, duplication, rearrangement, and

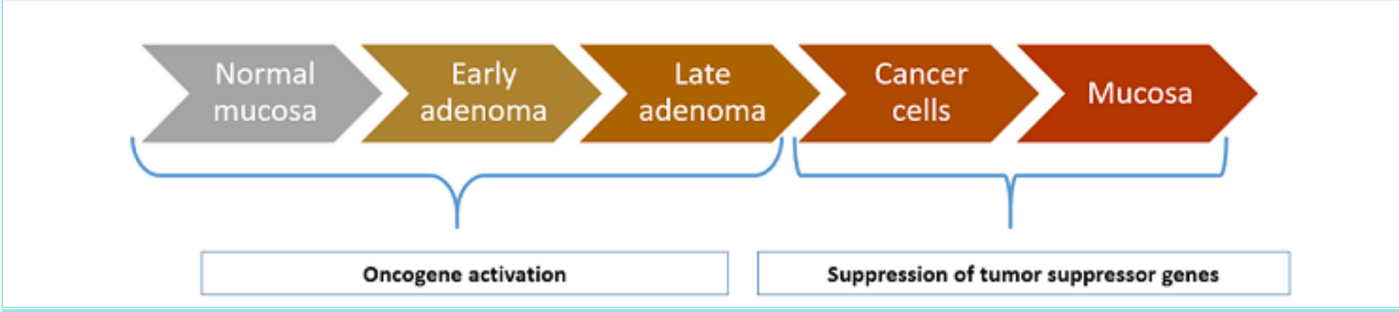

Figure 1. Colorectal cancer development.[4]

translocation are associated with CIN. Microsatellite instability is associated with incompatible DNA repair (MMR) and the silencing of tumor suppressor genes such as *p53* and *MLH1* as a result of hyper-methylation.[19]

Molecular Mechanisms Contributing to the Development of Colorectal Cancer

There are three main mechanisms for CRC carcinogenesis. The first of these is the suppressor pathway or CIN pathway put forward by Fearon and Vogelstein[20] in 1990. Activation of KRAS, an oncogene, and the suppression of tumor suppressor genes APC, SMAD4, and p53 are observed in this pathway. These molecular changes cause neoplastic transformations.[20,21] The second mechanism is also known as the mutator pathway or the micro-satellite instability pathway. The formation of CRC is due to errors which occur during DNA replication and mutations in repair genes (mismatch repair genes). These anomalies occurring in repetitive DNA fragments (micro-satellite) cause mutations in many genes involved in many cancer prognosis and accelerate tumor formation.[21] Another mechanism which plays a role in CRC formation is known as the epigenetic pathway involving aberrant hyper-methylation. In this pathway, changes or silencing of gene functions is observed as a result of hyper-methylation. Methylation pathway tumors mostly affect women and the elderly. These tumors are often poorly differentiated and more likely to have BRAF mutations. If the methylation pathway is active in the person, it is known not to respond to 5-fluorouracil, which is one of the most important chemotherapy treatment methods in CRC.[21]

Molecular Mechanism of Apoptosis and the Importance of Apoptosis in Colorectal Cancer

In multicellular organisms, there is a homeostatic balance between the number of cells which increase with mitosis and the number of cells which are damaged or no longer needed. The mechanism which provides this balance is the apoptosis mechanism which comes into play with the detection of cellular abnormalities.[22] Apoptosis first attracted attention as a result of programmed cell death in some of the somatic cells during the normal development of a nematode *Caenorhabditis elegans*.[23] Apoptosis is regulated by the family of proteases known as caspase (cysteinyl, aspartate-specific proteases).[17,24] It is possible to categorize those caspases which manage apoptosis, also known as programmed cell death, into two groups; initiator caspases (caspase-8, -9) and terminating caspases (caspase-3, -6, -7).[22] Activation of terminating caspases irreversibly induces the activation of endonucleases, destruction of nuclear proteins and cytoskeleton, and the elimination of damaged cells by stimulating the expression of phagocytic ligands.[4,22] Apoptosis is activated on many intracellular and extracellular signaling pathways.[25] One of these pathways is the intrinsic pathway, also known as the mitochondrial pathway, and the other is the extrinsic pathway, also known as the death receptor pathway.[25] The intrinsic (mitochondrial) apoptotic pathway is stimulated in response to situations such as DNA damage, activation of oncogenes, insufficiency of growth factors or the presence of oxidants. Oligomerization of the BAX and BAK proteins causes the mitochondrial membrane to become permeable and causes leakage into the intermembrane space of the intra-membrane second mitochondria-derived caspase activator (SMAC), cytochrome-c. As a result of cytochrome-c release; together with cytochrome-c, apoptotic proteinase activating factor-1 (APAF-1), dATP, and pro-caspase-9, the apoptosome is formed. Conversion of the procaspase-9 in its apoptosome to caspase-9 enables the induction of the terminating caspases (caspase-3, -6 and -7) and cell death.[22,26]

Ligands which are placed in the extrinsic or death ligand apoptotic pathway are Fas-ligand (Fas-L) and TNF-associated apoptosis-inducing ligand. The binding of the ligands to the receptor causes the death regions (FADD, TRADD) in the cytosolic part to bind to the procaspase-8 and -10 and the formation of a signal complex (DISC), which causes intracellular death. Formation of the DISC complex causes caspase-3, -6, and -7, terminating caspases activation and so triggers cell death.[22,27]

Apoptosis is a form of cell death necessary for tissue homeostasis, embryonic development and immune regulation.[28] The reduction of apoptosis or the development of resistance to apoptosis, which is important for the elimination of malignant cells and suppression of tumorigenesis, is the most important factor contributing to carcinogenesis.[29] In general, the impaired balance of pro-apoptotic and anti-apoptotic proteins decreased caspase function and impaired death receptor signaling are changes that can be seen in cancer cells.[29] The changing mechanisms associated with apoptosis which contribute to cancer development can be summarized as follows;

- Decreased death receptor expression,
- Reduced death signaling,
- p53 mutation,
- Decreased caspase expression,
- Impaired Bcl-2 protein family balance,
- An increase in anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1, Bcl-w),
- A reduction in pro-apoptotic proteins (Bid, Bim, Puma, Noxa, Bad, Bax, Bak),
- Increased apoptotic protein inhibitor expression.[28]

In the development of colon cancer, the inability or interruption of the apoptosis mechanism has molecular importance. In colon cancer, there is an imbalance between the number of cells renewed and the number of cells which die. This imbalance can be explained by increased proliferation.[29] Over time, the cell cannot respond to dangerous signals resulting from mutations with apoptosis, and this causes malignant transformations. While proliferation occurs more than necessary in CRC formation, apoptosis occurs less frequently.[28]

PRO-Apoptotic and Anti-Cancer Effects of Quercetin

Quercetin is a polyphenolic compound in the flavonol group of flavonoids. Vegetables, fruits and beverages such as onions, apples, strawberries, broccoli, tea and red wine are considered rich sources for quercetin. Quercetin can be found in foods in free (aglycone), carbohydrate (quercetin glycoside) or alcohol forms (quercetin methyl ester).[30] It is thought that there is an estimated 3-40 mg of quercetin intake per day in Western diets, and this rate may increase to 250 mg in societies with high vegetable and fruit consumption.[31] The quercetin contents of some foods in our daily diet are given in Table 1.

Quercetin is a powerful antioxidant and lipid peroxidation inhibitor, thanks to its catechol and hydroxyl group configuration, its capacity to scavenge free radicals and to bind metal ions.[32,33] Quercetin exerts an

anti-inflammatory effect by suppressing the NF-kB transcription factor responsible for the expression of COX-2 enzyme and pro-inflammatory cytokines. Quercetin has the potential to exert an anti-cancer effect by inhibiting important signaling pathways in carcinogenesis such as MAPK, JAK-STAT, and PI3K-Akt. In addition, it may show a potential inhibitory effect on cancer proliferation by inducing p53 activation in cancer cells (Figure 2).[33]

Quercetin is a lipophilic compound which can cross the cell membrane and activate multiple intracellular signaling pathways in chemoprevention.[32] The best known effects of quercetin are its dual function as a pro-oxidant or anti-oxidant. Oxidative stress caused by ROS species causes DNA damage and mutation development. Mutations are effective in hyperplasia and the proliferation of malignant tumor cells. Quercetin can reduce ROS by exchanging electrons and thus has the potential to prevent ROS-mediated DNA damage. In addition, quercetin can induce apoptotic pathways by showing cytotoxic and pro-oxidative effects.[32,33]

Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in mitochondrial membrane potential. In addition, quercetin also induces apoptosis through the activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, and caspase-9, and also the inhibition of anti-apoptotic proteins such as Bcl-2.[32,33] Quercetin increases the expression of cyclin-dependent kinases and cyclin B1 inhibitors p21, p27 and the tumor suppressor gene *p53*, which are involved in the cell cycle, and induces the cell to stop its cycle in the G1 and G2/M phases, thereby inhibiting cancer proliferation.[29] Heat shock proteins (HSPs) are proteins known to increase under stressful conditions such as wound healing, tissue repair, and carcinogenesis. Studies have shown that overexpression of HSPs, particularly HSP27, is closely associated with poor prognosis in many types of cancer. These proteins can affect cancer cell proliferation, invasion, differentiation, metastasis, and cell death.[34,35] It is thought that quercetin inactivates protein chaperones by inhibiting kinases which contribute to the induction of HSPs. Therefore, it is thought that quercetin can be applied as a supplement in cancer treatment in combination with existing chemotherapies.[29]

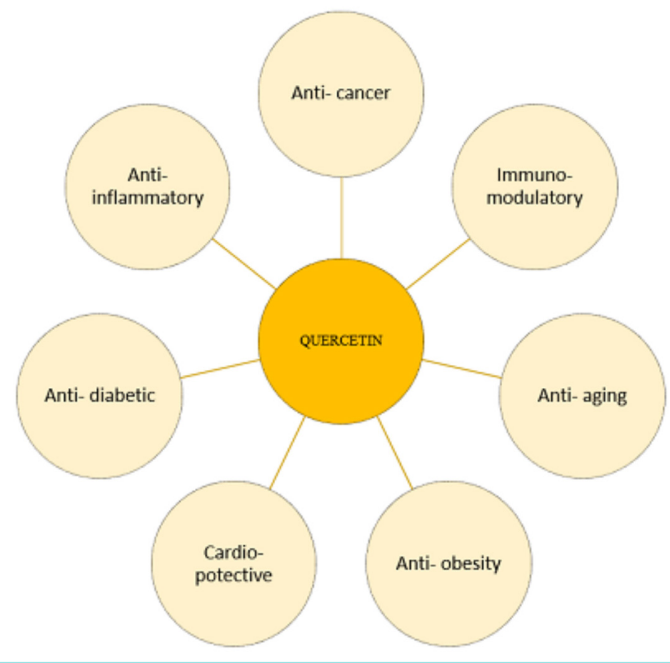

Figure 2. Health effects of quercetin.[31]

Experimental studies have demonstrated that quercetin affects the cell viability on different cell lines and colon cancer cell lines.[27,36-39] Özsoy et al.[6] conducted a study with two colon cells of different origins, primary and metastatic colon cancer cell lines, and demonstrated that the effective dose and incubation time was 25 µg/mL quercetin for 48 hours in both the Colo 320 and Colo 741 colon cancer cell lines. Their study showed that quercetin induced apoptosis which is the biological process cells use to achieve homeostasis and it plays a critical role in eliminating cancer cells.[6] Apoptosis is governed by initiating caspases (caspases-8, -9) and terminating caspases (-3, -6, -7). Anti-apoptotic proteins such as Bcl-2, Bcl-XL, and Bcl-w and also pro-apoptotic proteins such as Bax, Bak, Bid, and Bim are proteins involved in both the intrinsic and extrinsic apoptosis pathways.[22] Afrin et al.[40] and Soykut et al.[41], in their studies on different colon cancer cell lines, found the result that plant extracts rich in quercetin content trigger apoptosis in colon cancer cells. Afrin et al.[40] showed that while terminator caspase-3 levels increased in the LoVo metastatic colon cancer cell line after the application of manuka honey, which contains quercetin, levels of the anti-apoptotic protein Bcl-2 decreased. Becer et al.[42] revealed that quercetin was the dominant polyphenolic compound in the content analysis of molokhiya (*Corchorus olitorius* L.), a local food in Cyprus, and reported that apoptosis was triggered after the application of *Corchorus olitorius* L. extract. An *in vitro* study investigating the pro-apoptotic effects of quercetin in Colo 320 and Colo 741 colon cancer cell lines found that the effects of quercetin on apoptosis may differ depending on the cell type and it is more effective in primary (Colo-320) colon cancer cell lines.[7] Yang et al.[43], in their study on the HT-29 colon cancer cell line, determined that after 48 hours of 81 µM quercetin administration, anti-apoptotic Bcl-2 levels decreased, pro-apoptotic Bax levels increased, and the terminator caspase-3 levels increased and apoptosis was triggered. In another study, the colorectal adenocarcinoma cell lines HCT15 and HT-29 were compared. Cell viability of HT-29 cells was found to be lower as a result of incubation with quercetin. It was found that apoptosis was induced only in HT-29 cells, and that the activation of caspase-3 and cytochrome-c increased significantly. According to the results of that study, it was noted that increased intracellular ROS production and *COX2* gene expression may induce apoptosis.[44] In addition, in another study where the *in vivo* and *in vitro* pro-apoptotic effects of quercetin were examined in a dose and time dependent manner, the results reported that quercetin induced apoptosis in CT-29 (mouse colon cancer) cells (120 µM). In subsequent *in vivo* experiments, quercetin reduced tumor growth and increased survival rates when given in high doses (100-200 mg/kg).[45]

Table 1. Quercetin content of some foods[46]

Food	mg/100 grams
Onion	11-41.90
Lettuce	40.27
Tea	2
Apple	2.0-5.0
Cherry	1.0-3.0
Tomato	1.6
Broccoli	4.25
Asparagus	7.0-20.0

CONCLUSION

The studies presented suggest that quercetin has potential positive effects in CRC therapy. Various experiments have shown numerous action mechanisms which could inhibit multiple oncogenic signaling. Quercetin is a safe polyphenolic compound with no reported toxicity at cellular level in studies. Quercetin has beneficial biological effects with great potential to be used as an alternative therapy for colon cancer. However, additional clinical studies are needed for the further investigation of the mechanisms of quercetin to determine its role of suppression and intervention of cancer and possible use as an alternative colon cancer therapy.

MAIN POINTS

- Experimental research supports that quercetin can trigger apoptosis in colorectal cancer cell lines at different doses and incubation times.
- Quercetin may be effective in integrated cancer treatment by affecting cell death.
- Quercetin may provide the future for chemo-preventive drug development.

ETHICS

Peer-review: Externally peer-reviewed.

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Concept: S.Ö., G.S., E.B., Design: S.Ö., G.S., E.B., Supervision: S.Ö., G.S., E.B., Fundings: S.Ö., G.S., E.B., Data Collection and/or Processing: S.Ö., G.S., E.B., Analysis and/or Interpretation: S.Ö., G.S., E.B., Literature Search: S.Ö., G.S., E.B., Writing: S.Ö., G.S., E.B., Critical Review: S.Ö., G.S., E.B.

DISCLOSURES

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RESEARCH ARTICLE

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Determinants of Levothyroxine Treatment in Patients with Hypothyroidism

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Abstract

BACKGROUND/AIMS: Hypothyroidism is a common disorder. Thyroid dysfunction and treatment failure can cause major health problems. Levothyroxine is the only treatment available for hypothyroidism. Its effectiveness depends on several factors. In this article, we aimed to determine which factors can cause hypothyroidism and how they affect its treatment.

MATERIALS AND METHODS: One hundred and eighty subjects with hypothyroidism who were referred to an endocrinology outpatient clinic were enrolled in this study. The patients were grouped according to treatment effectiveness. These groups were compared in terms of age, gender, medication adherence, thyroid autoantibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (TG)], and thyroid heterogeneity. Co-ingested medications were investigated, and treatment effectiveness was compared.

RESULTS: The mean age was 46.8±12.8 years. One hundred and nine out of 162 patients were female (67.2%). Treatment failure was 55.6% (90/162). Patients with inadequate adherence to their levothyroxine treatment had higher anti-TPO and anti-TG levels (p=0.01). Ninety-three out of 162 patients (57.4%) had a medium/high adherence to levothyroxine therapy. Patients with low adherence (42.6%) experienced a higher treatment failure rate (p=0.01). Treatment failure rates did not vary according to gender or thyroid sonographic heterogeneity (p=0.49; p=0.66). Thirty-four out of 162 patients (21%) used medications which altered thyroid function. Additional medication use had an insignificant effect on thyroid-stimulating hormone levels (p=0.32).

CONCLUSION: These findings demonstrate high treatment failure rates, and that levothyroxine treatment adherence is an important subjective factor to determine treatment efficacy. Clinicians and patients should focus on underlying factors in order to increase treatment success.

Keywords: Hypothyroidism, levothyroxine, adherence, treatment efficiency, endocrinology

INTRODUCTION

Hypothyroidism affects a considerable fraction of the world population. Its prevalence varies according to country, gender, race, iodine status, region, and age group.[1] The prevalence of hypothyroidism is 24% in older adults (>65 years) in a United States population-based atherosclerosis risk in communities cohort.[2] According to a meta-analysis in Europe, thyroid dysfunction incidence in European countries is 5%.[3] The thyroid gland has important regulator, coordinator, and integrator roles in the body, and failure of treatment can result in serious health problems and, eventually, death.[4]

Levothyroxine is the only treatment choice for hypothyroidism. However, this treatment has several aspects to consider. Medication form (tablet, capsule, or liquid), patient adherence, and dosage times are the main considerations. Accompanying diseases and co-administered medications can interfere with levothyroxine absorption. The treatment of hypothyroidism depends on several factors. To avoid future health

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problems, such factors should be studied in order to have an effective treatment.

Therefore, in this study, we aimed to investigate levothyroxine treatment success rates in patients with hypothyroidism and to identify the influence of certain factors on treatment effectiveness.

MATERIALS AND METHODS

One hundred and eighty patients with hypothyroidism who were referred or admitted to the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinic of Endocrinology Outpatient between February, 2021 and January, 2022 were enrolled in this study. Their medical history was recorded, including age, gender, levothyroxine start time, dosage, operation history, accompanying diseases, and medication background. All laboratory examinations were carried out in the same laboratory. After overnight fasting before ingesting levothyroxine, a qualified laboratory staff-member took thyroid-stimulating hormone (TSH) and free T4 samples. TSH and free T4 were measured using the chemiluminescence method.

Additionally, other medications taken with levothyroxine and the place where levothyroxine was stored were investigated. The following patients were excluded: those who had chronic renal or hepatic failure; those diagnosed with malabsorption syndrome; malignancy; malignant thyroid disease; hypothyroidism after subacute hypothyroidism; central hypothyroidism; radioactive or drug-induced hypothyroidism; infiltrative disease associated with hypothyroidism; and pregnant patients. After exclusion, 162 patients were eligible for this study.

Levothyroxine adherence was measured using the validated Turkish version of the eight-item Morisky-Green test. This was performed by conducting face-to-face interviews. The patients were grouped according to their Morisky Medication Adherence Scores-8 [low adherence (<6); medium/high adherence (≥6)].[5-8]

Euthyroidism was defined as TSH levels between 0.4-4 mIU/mL. Patients with target TSH levels were compared with those patients with out-of-range TSH levels. The patients' age, gender, medication adherence, thyroid autoantibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (TG)], and thyroid heterogeneity in ultra-sonographic examination were compared in terms of achieving their treatment goals.

Ethical approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2021/2699). Written informed consent was obtained from all the patients. This study was conducted according to the Declaration of Helsinki principles.

Statistical Analysis

Statistical evaluations were performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences software version 22.0). Descriptive results are expressed as median (minimum-maximum) or mean ± standard deviation and percentages (%). Shapiro-Wilk test was used for normality. The chi-square test or Fisher's exact test was used for categorical variables, where appropriate. Student's t-test was used for comparing the normality of distributed continuous variables of the two groups. The Mann-Whitney U test was used for comparing continuous variables that were not normally distributed between two groups.

Logarithmic transformation was used for continuous variables which were not normally distributed. Spearman correlations were used to investigate the relationships between different variables.

RESULTS

The mean age of the patients was 46.8±12.8 years. One hundred and nine out of the 162 patients were female (67.2%). Forty-nine out of the 169 patients (36%) used levothyroxine after undergoing a thyroid operation (Table 1). No difference was found in the treatment effectiveness between those patients who underwent thyroid operations and those who did not undergo thyroid operations (p=0.11). The treatment failure rate was 55.6% (90/162) for all patients. Those patients who experienced treatment failure had higher anti-TPO and anti-TG levels (p=0.01). Ninety-three out of the 162 patients (57.4%) had a medium/high adherence to levothyroxine therapy. Patients with low adherence to levothyroxine had a higher rate of treatment failure (p=0.01) Treatment failure did not vary in terms of gender or thyroid sonographic heterogeneity (p=0.49; p=0.66) (Table 2). According to our survey, 94.4% (153/162) of the patients used levothyroxine properly, half an hour before breakfast. 86.4% (140/156) of the patients kept their supply of levothyroxine at room temperature. Thirty-four out of the 162 patients (21%) used medications which altered thyroid function (Table 3). Those patients who used other medications had non significantly different TSH levels (p=0.32).

DISCUSSION

This study showed that the treatment failure rate in Turkish patients with hypothyroidism was relatively high (55.6%). According to the TSH levels in each patient, we demonstrated which factors determined the success of hypothyroidism management. We found that age, thyroid antibodies,

Table 1. General properties of the study group

Characteristic	Mean/frequency
Age (mean)	46.8±2.8
Male/female	53/109
Target level	52/162 (32.1%)
Treatment failure	90/162 (55.6%)
Over treatment (TSH <0.1 mIU/L)	7/162 (4.3%)

TSH: thyroid-stimulating hormone.

Table 2. Differences between euthyroid patients and patients who experienced treatment failure

	Euthyroid	Treatment failure	p
Age (years) (n=155)	49.08±12.8	44.1±13.18	**0.04**
Male/female	22/44	30/59	0.79
TSH (mIU/L) (n=155)	2.71±1.50	7.90±3.44	**<0.01**
Free T4 (ng/L) (n=135)	4.24±4.44	3.77±4.07	0.63
Anti-TPO (IU/mL) (n=128)	154.9±220.6	497.73±630.2	**0.01**
Anti-TG (IU/mL) (n=120)	159.9±335.8	692.13±197.6	**0.01**
Thyroid ecogenity	32/42	67/90	0.66
Adherence (medium/high)	37/49 (64.1%)	48/87 (55.1%)	**0.03**

Significant values were expressed in bold, anti-TPO, and anti-TG.
TSH: thyroid-stimulating hormone, anti-TPO: anti-thyroid peroxidase, anti-TG: anti-thyroglobulin.

and treatment adherence were the factors which determined the success of hypothyroidism treatment. Our study included a broad evaluation, in which all factors involved in levothyroxine treatment were evaluated.

A study in Colorado examining 25,862 patients found that 40% of patients taking thyroid replacement therapy had out-of-range TSH levels.[9] Another study in India found that 41.7% of patients were undertreated.[10] It is important to understand what the reasons for the high treatment failure rate is. Our study tried to answer this question by evaluating several factors. The available treatment choice for hypothyroidism is levothyroxine tablets, and they are available only in capsule form in many countries. Levothyroxine is absorbed 20-30 minute after tablet intake and it takes nearly three hours to finalize its absorption stage.[8] Therefore, any factor which disrupts this process should be considered. We concluded that treatment adherence is one of the most important factors. We observed that, in those patients who failed in achieving their treatment goals, their treatment adherence was significantly lower (55.1%), whereas, in the sufficiently treated group, treatment adherence was 64.1% (p=0.03). In all study groups, treatment adherence was 57.4%. In a study examining 289 patients, 72.2% had a medium/high adherence to levothyroxine.[11] In another study, this ratio was 85.8%. However, these studies did not compare their adherence ratios with therapeutic effectiveness.

Despite low-medium adherence, we found that a high proportion of patients correctly obeyed the levothyroxine intake time. A majority of patients took levothyroxine at least half an hour before breakfast (94.4%). Several studies and reviews support the practice of delaying mealtimes for at least 30-60 minute after tablet ingestion.[12-14] A recent meta-analysis showed that levothyroxine intake half an hour before dinner was equally effective.[15] Another study which examined the effect of proton pump inhibitors (PPIs) co-administration in patients with hypothyroidism showed that serum TSH levels increased with PPIs.[16] Another study showed that calcium carbonate increased TSH levels in those patients using levothyroxine.[13] We found that a significant number of patients used medications which altered levothyroxine absorption or function (21.0%), but this did not affect TSH levels. According to another study, other medications did not affect TSH levels.[17]

Thyroid antibodies (anti-TG and anti-TPO) were significantly higher in the treatment failure group. Likewise, a study from Korea demonstrated that increased TPO antibody was found as a helper prognostic factor in subclinical hypothyroidism (SCH). In this study, high anti-TPO levels were associated with less improvement in thyroid function.[18] Although increased anti-thyroid antibody levels may indicate the likelihood of overt hypothyroidism, no correspondence of antibody level and risk for overt hypothyroidism has been found in most of the studies.[19] A study of 204 SCH patients showed sustained TSH elevation in patients receiving levothyroxine who had initially diffuse thyroiditis pattern in ultrasonography. Along with the anti-thyroid antibody positivity, the decline in thyroid functions increased.[20] The fact that anti-TPO antibodies not only elevate oxidative stress and glycosylation products, but also damage thyrocytes and block enzyme activity could explain these findings.[21] Therefore, high anti-thyroid antibodies could cause inflammation to become more severe and these patients may require higher doses of levothyroxine.

Table 3. Additional factors in treatment

Subjective factors	Frequency
Levothyroxine time (at least half an hour before breakfast)	153/162 (94.4%)
Levothyroxine storage place (room temperature, far from sunlight)	140/156 (86.4%)
Use of medications altering levothyroxine absorption	34/162 (21.0%)
Use of medications which do not alter levothyroxine absorption	39/162 (24.1%)

Study Limitations

The limitations of this study include the following: 1) dietary habits and ingredients were not evaluated; 2) this was a single-center and cross-sectional study. However, it included a significant number of patients and evaluated multiple factors in hypothyroidism treatment.

CONCLUSION

These findings demonstrate high treatment failure, and that adherence to levothyroxine treatment is an important subjective factor in determining treatment efficacy. Thyroid autoantibody levels and age were significant factors as well. Clinicians and patients should focus on underlying factors in order to increase treatment success.

MAIN POINTS

- Treatment success in patients with hypothyroidisim depends on several factors.
- 180 patients with hypothyroidism have been included in the study.
- Co-administered medications didn't seem to affect treatment success in hypothyroid patients
- Levothyroxine adherence was lower and thyroid auto antibodies were higher in the in patients who have not achieved treatment levels.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee for Clinical Research of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2021/2699).

Informed Consent: Written Informed consent was obtained from all the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., Y.H., Design: S.K., Y.H., Data Collection and/or Processing: S.K., Y.H., Analysis and/or Interpretation: S.K., Literature Search: S.K., Writing: S.K.

DISCLOSURES

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

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RESEARCH ARTICLE

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A Comparative Study on the Effects of B Massage and Entonox Gas on Pain Severity and Some Outcomes During Childbirth in Nulliparous Women: A Randomized Clinical Trial

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Abstract

BACKGROUND/AIMS: Reducing the intensity of labor pain is a way of encouraging women to select vaginal birth. The present study aimed to compare the effects of B massage and Entonox gas on pain severity during childbirth.

MATERIALS AND METHODS: This randomized clinical trial was conducted on 90 nulliparous women randomly selected from among those who were admitted for childbirth in Shahrivar Hospital of Saveh, Iran, from 6th August, 2015 to 13th April, 2016. Women with a gestational age of 37-42 weeks, a dilatation of 4-5 cm, and singleton pregnancy were selected. They were randomly divided into three groups as B massage, Entonox and control. The severity of pain was measured before the intervention and every 45 minutes after the first intervention using a visual analog scale. The data were analyzed by using chi-square, Tukey, Scheffe, Cramer and Spearman's correlation tests in SPSS software.

RESULTS: There was no significant difference between the three groups concerning their gestational age and their other demographic characteristics. ANOVA test showed lower pain intensity at 45, 90, 135, 180 and 225 minutes after the first intervention in the B massage group ($p<0.001$). Pain intensity was significantly lower in the massage group in the second stage of labor compared to the other two groups ($F3=15.61$, $df=2$, $p<0.001$). Chi-square test showed that cesarean section was more common in the Entonox group ($F3=13.123$, $p<0.001$), post-partum bleeding was more in the B massage group ($F3=8.535$, $p=0.014$) and newborn resuscitation was more frequently applied in the Entonox group ($F3=11.118$, $p=0.025$).

CONCLUSION: This study showed that B massage can reduce the intensity of labor pain but it increases post-partum bleeding and further studies on this type of massage are needed.

Keywords: Pain relief, massage, Entonox

INTRODUCTION

Reducing the intensity of labor pain is a way of encouraging women to select vaginal birth.[1,2] Pain relief during childbirth can reduce fear and anxiety leading to benefits in the childbirth outcomes. Childbirth pain is reduced by different methods which are divided into two main groups, namely pharmaceutical and non-pharmaceutical methods.[3,4] One of the pharmaceutical methods used to relieve labor pain is Entonox (nitrous oxide gas). This gas was first used by Wales in 1844 for analgesia.[5,6] Entonox is the equal mixture of 50% nitrous oxide and 50% oxygen. Administration of Entonox for analgesia is performed during the first and second stages of labor and its maximum effect appears

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within two minutes after use.[7] Entonox helps relieve short-term pain and also reduces anxiety and pain in a wide range of painful actions, such as drainage, lumbar puncture or dressing.[8] The advantages of using Entonox are that it is fast and effective, it leaves the body quickly and it is cost-effective. The disadvantages or complications of using Entonox are dry mouth, vertigo, lethargy, vomiting and uncomfortable feelings.[9] As self-administrated Entonox inhalation was used, the depth of breathing and the amount of gas used could not be evaluated. The patient's sense of being able to control pain may not only be related to the usage of Entonox, but also to their self-control of the drug. The use of Entonox during labor pain could be a step towards natural vaginal deliveries in Iran where many women tend to undergo caesarian section. Factors that limit Entonox's acceptability include confusion, sleepiness, an unwillingness to use a mask and feelings of pain after stopping gas inhalation.[9,10]

Nowadays, non-pharmacological methods of pain relief as a safe method have been widely used around the world and it is primarily based on empowering mothers. One of these methods is massage therapy, which in addition to relieving labor pain, leads to more communication with the mother, strengthens the effects of relaxation and reduces emotional stress.[11] Several theories have been proposed to explain the mechanisms by which massage can alleviate pain, including lowering cortisol and norepinephrine levels,[12,13] and augmenting serotonin levels.[14] Many researchers believe that mechanical massage pressure can accelerate blood flow, thereby increasing metabolism and oxygen supply.[15] A five-minute massage on the waist can increase skin blood flow, blood volume muscle and lymph circulation. As a result, excretion of toxins and residual materials improves and nutrient flow to tissues increases and so reduces swelling and pain.[16,17] In addition, Melzak and Wall[18] proposed a mechanism whereby creating a stimulus which interferes with the transmission of pain to the brain, effectively "closes the gate" to the reception of pain.

Various massage techniques such as massage all over the back (Swedish massage), massage of the buttocks (Linda Kimber's massage) and the massage of the lower back and buttocks (B massage) are used during labor.[19,20] There are many studies which have shown that Entonox gas and massage affect the severity of labor pain, however, little information is available about B massage and its comparison with Entonox. Therefore, the researcher decided to compare the effects of B massage and Entonox gas on pain severity and some outcomes type of delivery, the rate of augmentation of postpartum bleeding, newborn resuscitation during childbirth.

MATERIALS AND METHODS

This randomized clinical trial (IRCT 20180128038535N2) was performed on 90 nulliparous women in the delivery ward of 17 Shahrivar Hospital of Saveh, Iran from 6th August, 2015 to 13th April, 2016. The inclusion criteria were having their first pregnancy, a gestational age between 37-42 weeks, a singleton pregnancy, fetal head presentation, dilatation of 4-5 cm or more (active phase of the first stage of labor) and an anesthesiologist prescription for the Entonox group. High risk pregnant women (pre-eclampsia, eclampsia, diabetic women, those with chronic disease, those with cardiovascular disease etc.), pre-rupture of the membrane, pre-term labor, induction of labor, drug abuse or those who had skin or lumbar problems in the lower back in the massage group were not enrolled into this study. The exclusion criteria were dissatisfaction with continuing the study, any problems requiring medical intervention, birth occurring within 225 minutes after starting the study, and using any pharmacological or non-pharmacological analgesics except for B massage or Entonox gas during the study. The cases were divided into three groups, namely B massage, Entonox gas and control. After explaining the study, 30 women were randomly selected in each group based on the confidence interval of 95% and power of 80% (Figure 1). To allocate the women randomly, numbered cards (1-3) were used. The cards were placed inside envelopes and the participants had to choose one of them. If they chose numbers 1, 2, 3, they were placed in the B massage, Entonox or the control groups respectively.

In this study, the researcher used observation, examination and questionnaire to collect the essential data. The questionnaire consisted of three parts: the first part related to the demographic characteristics, (occupation, education, location, residence statue), the second part was delivery information (type of delivery, need of augmentation, postpartum hemorrhage, newborn resuscitation), and the third section was information corresponding to the pain intensity just before the intervention and at 45, 90, 135, 180 and 225 minutes after starting the study or the first intervention. Also, pain intensity was measured at the second stage of labor. Pain severity was measured using McGill's visual analog scale (VAS). Numbered cards (1-3) were used to randomly allocate the three groups. In the B massag[20] group, at dilatation of 4-5 cm, the participant was placed on their side or standing when the abdominal stiffening was declared by the mother so that she leaned forwards with her hands on the bed. The researcher was positioned behind and to the left or right of the mother. As soon as the abdomen tightened, with the palm of the hand, the massage was started from the lower back of the waist, moving from one side to the other, and moving the hand down the buttocks, and from the gap between the two buttocks moving up and then down. The massage is actually in the form of the letter B, the straight line is along the lower back and the two rings are on the two buttocks. The massage started from dilatation 4-5 cm and continued until the end of the first stage of labor. The massage began at the beginning of each uterine contraction and continued until the end of the contraction. Continued use of B massage in the second stage of labor depended on the mother's desire (Figure 2).

In the Entonox group (following the order of an anesthesiologist), at a dilatation of 4 to 5 cm, the unit of study was given an explanation and training on how to use Entonox gas and the time it was to be used. The patient was told by the researcher to put her hand on her abdomen, and as soon as the abdominal stiffness began, she administered Entonox through a facemask which was attached to a one-way valve which enabled the patient to breathe gas with each inhalation. Inhalation of the gas was carried out in the form of a deep and calm breaths, and this inhalation continued until the end of the pain. When using Entonox gas, the researcher was positioned next to the individual and helped her during the intervention. In the Entonox group, gas inhalation was begun by the mother at the beginning of each uterine contraction and continued until the end of each contraction. Continued use of Entonox gas in the second stage of labor depended on the mother's desire.

The control group received standard care according to the protocols of the Ministry of Health. The information about the type of delivery, Apgar scores for the first and the fifth minutes, the need for resuscitation of the newborn, the amount of excessive hemorrhage (estimated more than 500 cc) according to the need for checking hemoglobin in the first

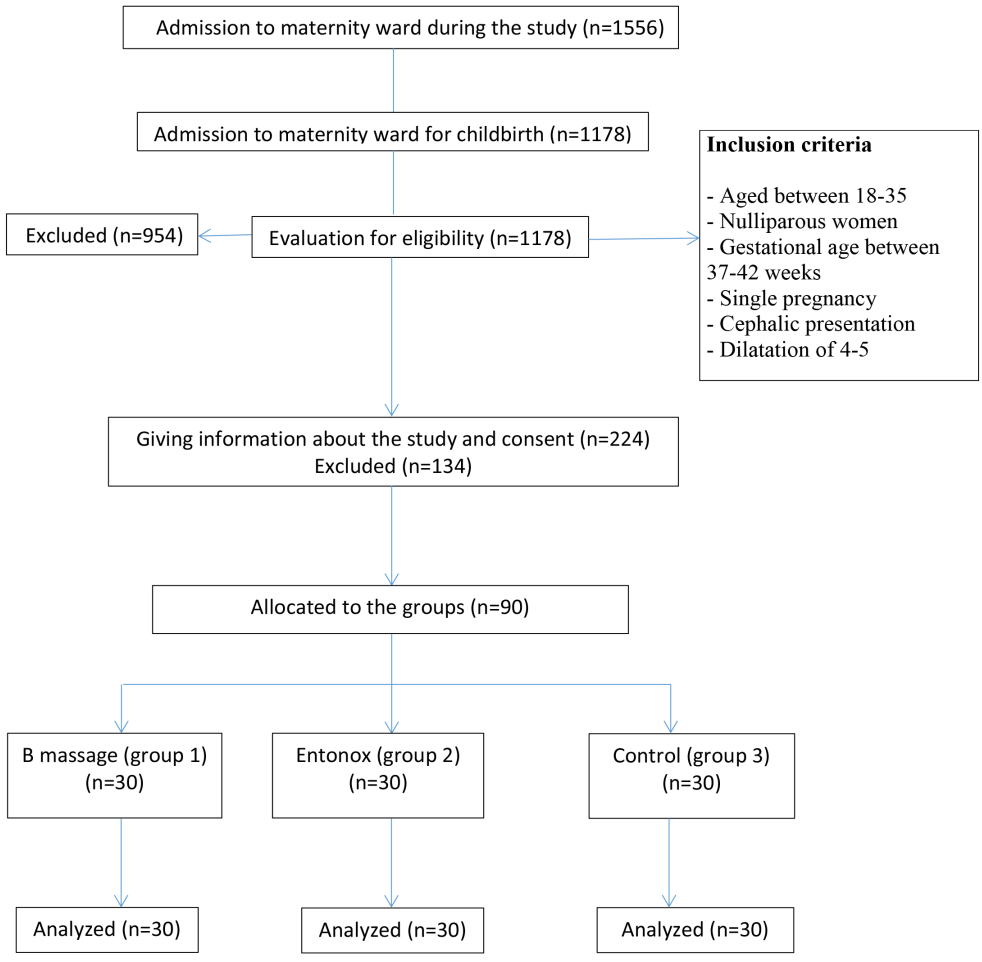

Figure 1. Consort flow diagram.

6 hours postpartum, blood transfusion, as well as the need for using misoprostol were collected and recorded via a questionnaire.

Statistical Analysis

Chi-square, Scheffe, Tukey, Cramar and Spearman correlation tests were used for data analysis in SPSS software (version 15; SPSS software, Chicago, IL, USA). All p-values less than 0.05 were considered significant.

Ethical Considerations

Ethical approval was obtained from the Human Research and Ethics Committee of Saveh University of Medical Sciences, (approval number: IR.SAVEHUMS.REC.139401). Prior to this study, all the mothers provided written informed consent and the study method was described in detail for all participants. A separate room was used for the comfort and privacy of the mothers and emotional communication was established for the three groups at all the stages of this study.

RESULTS

Among the 90 pregnant cases studied, their mean age was 28.31 (7.17) years in the B massage group, 29.43 (5.77) years in group of Entonox and 28.12 (4.81) years in the control group. Mean gestational age

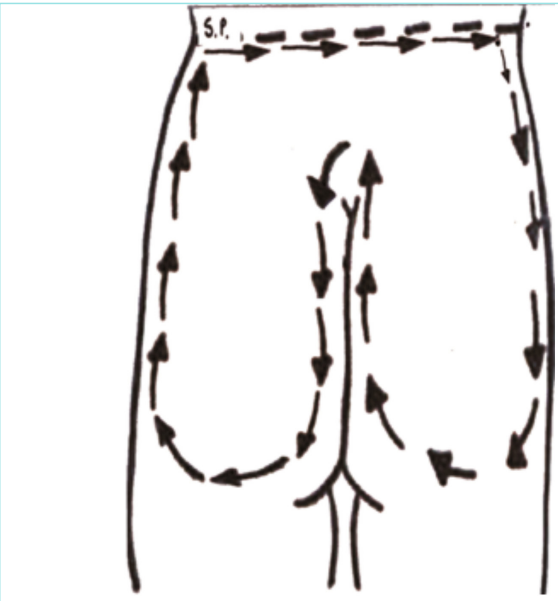

Figure 2. B massage protocol.[19]

based on the first day of menstruation and sonography of the first trimester were 39.08 (0.92) and 39.04 (0.93) weeks in the B massage group, 39.77 (1.02) and 39.70 (0.87) in the Entonox group and 39.16 (1.36) and 39.06 (1.34) weeks in the control group, respectively. There was no significant difference in the maternal age between the three groups (F=0.371, DF=65, p=0.692), gestational age (based on the first day of menstruation, (F=0.205, DF=60, p=0.138) and sonography of the first trimester (F=2.318, DF=61, p=0.107). The economic status, level of education and other demographic characteristics are shown in Table 1.

As seen in Table 2, the mean of pain severity on the VAS before the intervention was not significantly different between the three groups. However, 45 minutes after starting the study (or after the first intervention), pain severity was significantly less in the B massage and Entonox groups compared to the control group (p=0.001). Post-hoc test (Tukey test) showed no significant difference between the B massage and Entonox groups (p=0.177). Post-hoc test (Tukey test) showed no significant difference between the Entonox and control groups 90 minutes after the first intervention (p=0.077). Post-hoc test showed pain severity was significant less in the Entonox group compared to the control group at 135, 180 and 225 minutes after the first intervention (p=0.001). Pain intensity in the second stage of labor was significantly lower in the B massage and Entonox groups. Post-hoc test showed no significant difference between these two groups (p=0.834). The difference between the mean scores of pain intensity in the first stage of labor was significantly different between the three groups (confidence interval 95%) (df =2, F=13.409, p=0.001) and the mean pain intensity in the control group was more than the two other groups. The difference between the mean scores of pain intensity in the second stage of labor was significantly different between the three groups and the mean pain intensity in the control group was more than the other two groups (confidence interval 95%) (df =2, F=19.106, p=0.001).

Mann-Whitney test showed that the severity of pain in the first stage of labor was not significantly different between the three groups according to the need for newborn resuscitation (p=0.12). The Mann-Whitney test showed that the severity of pain in the first stage of labor was not significantly different between the three groups in terms of postpartum hemorrhage (p=0.17). The Mann-Whitney test showed that the severity of pain in the first stage of labor was not significantly different between the three groups in terms of the first and fifth minute Apgar scores (p=0.19). There was no significant difference between the three groups in terms of the rate of augmentation (p>0.05). There were significant differences between the three groups in terms of the type of delivery,

Table 1. Frequency distribution of demographic characteristics

Demographic characteristics		B massage, n (%)	Entonox, n (%)	Control, n (%)	Chi- square	df	p-value
Mother's education	Illiterate	2 (6.7)	4 (13.30)	17 (56.70)	2.81	2	0.246
	Under diploma	14 (46.70)	4 (13.30)	9 (30)	-	-	
	Diploma	14 (46.70)	18 (60)	4 (13.30)	-	-	
	Academic	-	4 (13.30)	-	-	-	
Husband's education	Illiterate	5 (16.7)	-	1 (3.3)	1.30	2	0.522
	Under diploma	9 (30)	8 (26.70)	17 (56.7)	-	-	
	Diploma	16 (53.3)	18 (60)	11 (36.7)	-	-	
	Academic	-	4 (13.3)	1 (3.3)	-	-	
Mother's occupation	Housewife	30 (100)	30 (100)	28 (93.30)	1.02	2	0.602
	Employed	-	-	2 (6.70)	-	-	
Husband's occupation	Employee	4 (13.30)	20 (64.30)	6 (20)	0.85	2	0.653
	Self-employed	26 (86.70)	10 (35.70)	24 (80)	-	-	
Location	Urban	23 (76.70)	22 (73.30)	27 (90)	1.52	2	0.467
	Rural	7 (23.30)	8 (26.70)	3 (10)	-	-	
Residence status	Owner	16 (53.30)	17 (56.70)	10 (33.30)	0.77	2	0.680
	Tenant	14 (46.70)	13 (43.13)	20 (66.70)	-	-	

Table 2. The mean score of pain severity during childbirth (VAS)

Group	B massage, mean (SD)	Entonox, mean (SD)	Control, mean (SD)	F	df	p-value
Before intervention	5.69 (85)	5.71 (0.73)	5.18 (1.42)	1.80	2	0.173
45 minutes after intervention	4.38 (0.77)	5.05 (0.86)	5.47 (1.13)	5.70	2	0.005
90 minutes after intervention	3.69 (0.86)	4.86 (0.79)	5.56 (1.31)	13.91	2	0.0001
135 minutes after intervention	3.38 (0.51)	4.23 (0.99)	5.56 (1.26)	21.14	2	0.0001
180 minutes after intervention	3.08 (0.28)	4.05 (0.80)	5.41 (0.99)	41.41	2	0.0001
225 minutes after intervention	4.00 (0.00)	4.81 (0.68)	6.09 (1.11)	31.31	2	0.0001
Second stage of labor	5.17 (1.47)	5.50 (0.55)	7.67 (071)	15.61	2	0.0001

SD: standard deviation, VAS: visual analog scale.

Table 3. Frequency distribution of delivery type, augmentation, postpartum hemorrhage and newborn resuscitation

Group variable		B massage, n (%)	Entonox, n (%)	Control, n (%)	χ^2	df	p-value
Type of delivery	NVD[1]	30 (100)	28 (93.3)	30 (100)	13.123	2	0.001
	Cesarean section	0 (0.0)	2 (6.7)	0 (0.0)			
The rate of augmentation	Yes	17 (56.7)	14 (46.7)	10 (33.3)	2.700	2	0.259
	No	13 (43.3)	16 (53.3)	20 (66.7)			
Post-partum hemorrhage	No intervention	7 (23.3)	18 (60)	0 (0.0)	8.535	2	0.014
	Massage of uterus	18 (60)	12 (40)	30 (100)			
	Checked Hb[2]	5 (16.7)	0 (0.0)	0 (0.0)			
Newborn resuscitation	No resuscitation	20 (66.7)	9 (30)	30 (100)	11.118	4	0.025
	Stimulation of the newborn	10 (33.3)	17 (56.7)	0 (0.0)			
	Mechanical ventilation	0 (0.0)	4 (13.3)	0 (0.0)			

NVD[1]: normal vaginal delivery, Hb[2]: hemoglobin.

postpartum bleeding and new born resuscitation ($p<0.05$) (Table 3). Out of 90 cases in the three groups, two cases in the Entonox group underwent cesarean section due to fetal distress.

The mean neonate Apgar score in the first minute after birth was 8.66 (1.26) in the B massage group, 7.80 (0.40) in group of Entonox and 9.00 (0.00) in the control group. The mean neonate Apgar score at 5 minutes after birth was 9.80 (0.76) in the B massage group, 9.40 (0.40) in group of Entonox and 10.00 (0.00) in the control group. The mean Apgar score at the first and fifth minutes after birth was not significantly different among the three groups ($p>0.05$).

DISCUSSION

An exhaustive review of the relevant literature showed that there had not been any similar studies conducted previously which compared the efficacy of the implementation of B massage and Entonox on labor pain reduction and the outcomes of childbirth. Hence, the findings of the present study were compared with findings obtained in studies dealing with other similar massage techniques and the use of Entonox.

As previously specified, labor pain is a progressive process as it increases in severity with increasing dilation. In the present study, pain severity was less in the B massage group compared to the Entonox and control groups after the intervention. The reason may be due to the fact that massage stimulates large-diameter nerve fibers to wrinkle as the mechanism of cortex pain coverage which leads to pain relief.[21-26] In Janssen et al.[27] study titled "Massage therapy and labor results", 77 nulliparous women with spontaneous onset of labor were randomly divided into two groups, namely a Swedish massage group and a control group. The results showed that pain intensity in the intervention group was less than the control group, and in this regard, it is consistent with our study. In the study by Silva Gallo et al.[17] titled "Massage reduced the severity of labor pain (clinical trial)", 44 cases received massage by a physiotherapist for 30 minutes. The severity of labor pain after the intervention was statistically lower than the control group. Aghdam et al.[28] studied the effect of massage on the duration and severity of labor pain in nulliparous women. Their result showed that massage significantly reduced the severity of labor pain, which is consistent with our study. Sananpanichkul et al.[29] in their study titled the "Possible role of Court-Type Thai traditional massage during parturition: a randomized controlled trial", 59 cases were enrolled into c-TTM massage and control groups. They reported that there was no statistical difference of pain score during the intrapartum period between the two groups, which is not consistent with our study. Their research is a different procedure from the present study because c-TTM massage was applied only once in the active phase of labor.

Naddoni et al.[30], in their research, showed that the intensity of labor pain was significantly lower in the Entonox group compared to the oxygen group (60 and 120 minutes after starting the study) which is not similar to our study. Foji et al.[31] compared the effect of Entonox inhalation and spinal anesthesia on reducing labor pain. Their findings showed that spinal anesthesia was more effective than Entonox gas. In our study, the effect of Entonox on pain intensity was less, and in this regard, their result is consistent with our study. Masoudi and Akbari[32] compared the effect of Entonox and warm water for pain relief during childbirth. They found that the pain scores in the Entonox group was significantly lower than the warm water group. The similarity of our study with Masoudi and Akbari[32] study is the use of a non-pharmacological method in comparison to Entonox gas but, in our study, the pain intensity was lower in the non-pharmacological method (massage), and in this regard, their result is not consistent with our study.

In relation to the type of childbirth, our results show no significant difference between the three study groups. Bolbol Haghighi et al.[33] in her study reported no significant difference between the massage and control groups in terms of the mode of delivery. In the study of "the effect of Saninjiao point massage on the active phase of labor in nulliparous women", Kashanian et al.[34] reported that the rate of cesarean section in the massage group was significantly lower than the control group. Sananpanichkul et al.[29] reported no significant differences between the c-TTM massage and control groups in terms of cesarean section. Janssen et al.[27] reported that there was no statistically significant differences in the mode of delivery between the Entonox and control groups. In Parsa et al.[35] study in the type of delivery, there was no significant difference between the two groups of Entonox and control, which did not conform to our research results.

The rate of cesarean section in our study was 2.5% (only two cases in the Entonox group had cesarean sections). This can be both a weakness and a strength point of our study. In support of this, the American College of Obstetricians and Gynecologists have also found that active management of childbirth cannot reduce cesarean rates in all cases.[36] The World Health Organization in 1985 stated that an increase in cesarean section rates to 10-15% is not related to increases in maternal and neonatal

health and outcomes. In this study, continuous emotional support and one-on-one care for the mother and caregiver or midwife may have reduced the rate of cesarean section to less than 5%. On the other hand, reducing cesarean sections may have long-term complications which have not been studied in our research.

In relation to the need of augmentation (need of oxytocin), our results showed no significant difference between the three groups. In support of this finding, Bolbol Haghighi et al.[33] and Janssen et al.[27] also found no significant difference between the groups of massage and control for the need of oxytocin and augmentation.

In our study, the amount of postpartum bleeding was measured based on the need for uterine massage, checks for hemoglobin and no need for intervention. Many studies have shown that massage can improve and speed up blood circulation, thereby increasing muscle blood volume which may cause an increase in postpartum bleeding.[37,38] Agah et al.[39] in their research titled "the effects of continuous use of Entonox in comparison with intermittent method on obstetric outcomes: A randomized trial" reported that in 4% of the intermittent group, postpartum hemorrhage happened due to uterine atony in contrast to the continuous group in which post-partum hemorrhage was 0%; there was no significant difference (p=0.2). Also, they reported that uterine atony decreased with the continuous method, however, neither method was associated with massive postpartum hemorrhage. The similarity of our study with this research is in the intermittent use of Entonox. Similarly, Arthurs and Rosen[40], Esfandiari et al.[41], and Najefian et al.[1] stated that there was no severe postpartum hemorrhage due to uterine atony due to using Entonox. In the study of Sananpanichkul et al.[29], there was no significant difference between the massage and control groups for postpartum bleeding and also the rate of bleeding was in the usual range (200-300 mL).

33% of newborns in the group of B massage needed stimulation. Massage can increase vagal activity by lowering blood pressure, changing the heart rate and lowering cortisol levels, and so, excessive fetal activity is reduced.[37,38] This may have been the reason for the need of stimulation in the massage group. In the Entonox group, neonatal stimulation and mechanical ventilation were more frequent and 4 newborns needed resuscitation while no cases in the B massage or control groups needed resuscitation. Also, in the control group, none of the newborns needed the process of resuscitation.

Entonox has transient effects due to excretion from the lungs and has no significant side effects on the fetal cardiovascular, respiratory or nervous systems[42] so it is used as a healthy and safe method in home birth due to its lack of risk for the mother and fetus. However, it is possible that it actually causes fetal distress.[43] In our study, the Apgar score was lower and the rate of resuscitation was higher in Entonox group but these differences were not significant. Agah et al.[39] reported that the Apgar scores of neonates at the first and fifth minutes between the Entonox and control groups were acceptable and had no significant difference (p=0.3).

CONCLUSION

B massage has a greater pain relief effect compared to Entonox and it can be used as a method to reduce labor pain, but it increases post-partum bleeding. It is necessary to conduct more research on this type of massage and its disadvantages and advantages during childbirth.

MAIN POINTS

- One of the strengths of our study is its investigation of a type of massage that has been rarely studied.
- The second strength of this study was the comparison of three groups, which included both pharmacological and non-pharmacological methods.
- Another strength of this study is the estimation of postpartum hemorrhage. This variable has received little attention in other massage-related studies.
- An important conclusion to be understood from this study is that massage can affect the amount of postpartum hemorrhage. Although the amount of bleeding in our study was above the normal range, in future studies, special attention should be paid to the effects of massage on postpartum bleeding.
- One of the limitations of this study was that the research had to be designed based on the conditions of the delivery room and routine care.

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ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Human Research and Ethics Committee of Saveh University of Medical Sciences, (approval number: IR.SAVEHUMS.REC.139401).

Informed Consent: Prior to this study, all the mothers provided written informed consent and the study method was described in detail for all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.R., Design: Sh.D., Supervision: M.R., Fundings: Sh.D., Materials: M.R., Data Collection and/or Processing: M.R., Analysis and/or Interpretation: M.R., Literature Search: Sh.D., Writing: M.R., Critical Review: Sh.D.

DISCLOSURES

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

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RESEARCH ARTICLE

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Bariatric Surgery and Quality of Life in Obese Patients with Respiratory Difficulty

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Abstract

BACKGROUND/AIMS: Epidemiology shows that obese patients have high respiratory distress and other comorbid diseases in addition to low health-related quality of life (HRQL). The HRQL results were investigated after weight loss in a group of patients with repiratory distress who had undergone bariatric surgery in this study.

MATERIALS AND METHODS: Patients who presented to our clinic with respiratory distress before bariatric surgery were included in this study. One year after surgery, the patients were evaluated for improvements in comorbid diseases and the 36-Item Short-Form Survey (SF-36) Quality of Life Scale was conducted.

RESULTS: In his study, 120 obese patients with respiratory distress were included. The mean age of the patients was 41.28±1.06 years and the ratio of women to men was 70/30. Concomitant diseases included diabetes (61.6%), hypertension (47.5%), social maladjustment (40%), mental problems related to eating (38.3%), asthma (35%) and sleep apnea (27.8%). Postoperative clinical complaints decreased and the amount of drug use in patients relating to all diseases decreased. The SF-36 Quality of Life Scale mean scores of the patients were as follows: physical function (95±7.10), physical role (100±0.0), pain (92.3±10.1), emotional role (79.27±34.16), general health perception (80.3±16.4), energy-vitality (74±15.76), mental health (74.3±17) and social function (84.37±20.57).

CONCLUSION: There was a significant decrease in the clinical complaints and drug use of the patients after bariatric surgery. It was observed that the perception of HRQL was significantly higher. It has been observed that weight loss was beneficial in disease control and quality of life in the obese population. It can be recommended to those who cannot achieve weight loss via non-invasive approaches.

Keywords: Bariatric surgery, comorbid diseases in the obese population, quality of life in the obese population, respiratory difficulty in the obese population

INTRODUCTION

Obesity is a chronic disease of our era and is a cause for concern as a result of its multiple comorbidities. According to the World Health Organization, it is one of the ten highest risk diseases.[1] Respiratory difficulty is a common complaint in obese patients. In the literature, obesity has been recognized as a significant factor for asthma risk and its prognosis.[2] Obesity in patients may be accompanied by more than one comorbidity. Therefore, its treatment is difficult and complex.[3,4] In obese patients, more frequent doctor visits, increased medication use, longer hospitalization, and lower quality of life are observed.[5] The quality of life concept is increasingly being used in the field of health, as in every field.[6] People with extreme obesity face discrimination in society regarding their weight, which is associated with negative psychological consequences. Therefore, these individuals are more likely to experience depression, anxiety, body image dissatisfaction, and poor quality of life. The incidence of more than one chronic comorbid disease in the obese patient group is also one of the significant factors affecting their quality of life. The literature shows that improving the physical condition of obese patients improves comorbid diseases, psychosocial

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factors, and their health-related quality of life (HRQL).[7-9] Quality of life expresses happiness, satisfaction with life and general well-being; it is an important indicator of the success of health interventions.[8,10,11] The effect of a disease on the quality of life is related to the physical, psychological and social perceptions of the patient. Patient perception is usually measured using internationally accepted scales.

In the treatment of obesity, regular physical activity, healthy diet practices and non-invasive medical treatments are recommended. Morbidly obese patients who cannot lose weight through these methods can be referred for bariatric surgery.[12] Bariatric surgery is an invasive procedure which has the potential for complications.[13,14] Although the clinical benefits of bariatric surgery in comorbid diseases are known, less is known about its impact on psychosocial outcomes such as health-related quality. Clinical trials are still needed before recommending bariatric surgery for obesity treatment. In this study, the outcomes of effective weight loss with surgery on the presence of comorbidities and HRQL results in a group of patients who had undergone bariatric surgery were evaluated.

MATERIALS AND METHODS

A total of 120 obese patients who received consultation in our clinic for bariatric surgery were enrolled in this study. The common feature of the patients, which was important for our clinic, was that the patients had breathing difficulties. The targeted weight loss occurred in the patients 6-10 months after surgery. The necessary permission for this study was obtained from the Near East University Clinical Research Ethics Committee (approval number: YDU/2020/81-1133, date: 30.07.2020). One year after surgery, some of these patients were contacted for follow-up at the outpatient clinic and some by phone. After the patients were informed about this study, verbal consent was obtained from those who volunteered to participate. In addition to the demographic information of the patients, their accompanying comorbid diseases, the number of drugs used after surgery and the change in the frequency of their doses were recorded. Following this, the 36-Item Short-Form Survey (SF-36) Quality of Life Scale was administered to the patients. In this study, the postoperative improvement in diseases and drug use and the relationship between age, gender, education, marital status variables and quality of life were compared.

The SF-36 Quality of Life Scale is one of the scales most frequently used to determine quality of life.[15] The scale has 36 items which enable the measurement of 8 dimensions; physical function (10 items), role limitations due to physical functions (4 items), mental health (5 items), social function (2 items), role limitations due to emotional problems (3 items), pain (2 items), energy/vitality (4 items) and general health perception (5 items). The second question on the scale comprises the perception of health change in the last 12 months. Other questions are evaluated based on information from the previous four weeks. The fourth and fifth questions are evaluated as “yes” or “no”, while other questions are evaluated with Likert-type (3, 5 and 6) grading. The score is calculated by reverse scoring for several items of the scale.[15]

RESULTS

A total of 120 morbidly obese patients with respiratory distress were included in this study. The mean age of the patients was 37.4±9.9 years. The ratio of women to men was 70/30, and 55% of them were university graduates. The demographic information of the patients is presented in Table 1.

Of the patients participating in this study, 62.2% had diabetes, 48.1% had hypertension, 40% had social maladjustment, 38% had mental problems related to eating, 35% had asthma and 27.8% had sleep apnea. The comorbidities of the patients are presented in Table 2. After surgery, the clinical complaints relating to these diseases improved and there was a 57.1% decrease in the total number of drugs used for all diseases ($p<0.05$).

When the mean scores for the patients in the sub-dimensions of the SF-36 Quality of Life Scale were investigated, it was determined that physical function was 95±7.10, physical role was 100±0.0, pain was 92.3±10.1, emotional role was 79.27±34.16, general health perception was 80.3±16.4, energy-vitality was 74±15.76, mental health was 74.3±17.06 and social function was 84.37±20.57 (Table 3).

The mean scores in the sub-dimensions of the SF-36 Quality of Life Scale for some descriptive characteristics of the patients are presented

Table 1. Descriptive characteristics of the patients

Introductory features		
Age	**n**	**%**
18-25	6	5
26-35	34	28.3
36-45	48	40
46-55	14	11.7
56 and over	18	15
Total	120	100
Gender	**n**	**%**
Female	84	70
Male	36	30
Total	120	100
Education	**n**	**%**
Primary education	22	18.3
High school	32	26.7
University	66	55
Total	120	100
Marital status	**n**	**%**
Married	90	75
Single	30	25
Total	120	100

Table 2. Medical characteristics of the patients

Medical properties		
Chronic disease	**n**	**%**
Yes	92	76.7
No	28	23.3
Diabetes	74	61.6
Hypertension	57	47.5
Social maladjustment	48	40
Psychological problem with eating	46	38.3
Asthma	42	35
Sleep apnea	32	26.6
Some patients have more than one chronic disease.		

Table 3. Distribution of patients' scores from the SF-36 Quality of Life Scale sub-dimensions

SF-36 sub-dimensions	Mean ± SD	Lowest score	Highest score
Physical function	95±7.10	75	100
Physical role	100±0.0	100	100
Emotional role	88,95±16	66	100
Energy/vitality	74±15.76	40	100
Mental health	74.3±17.06	40	100
Social function	84.37±20.57	50	100
Pain	92.3±1.07	67.5	100
General perception of health	80.3±16.4	40	100

SF-36: 36-Item Short-Form Survey, SD: standard deviation.

in Table 4. When the mean scores in the SF-36 Quality of Life Scale sub-dimensions were investigated according to several descriptive characteristics of the patients, it was determined that the scores for physical health, general health (p=0.020), vitality (p=0.007) and mental health (p=0.003) of the patients in the 46-55 age group were statistically significantly higher. While physical health was good for patients under the age of 46, the average vitality, mental, social, and emotional health was lower than for those patients over 45 years old, which was statistically significant (p=0.049). There was no statistically significant difference between the mean scores of the SF-36 Quality of Life Scale sub-dimensions according to the education level of the patients (p>0.05). According to the gender of the patients, the average scores for vitality and mental health were lower in females, while they were close to each other in the other parameters (p<0.05). While there were no disparities in physical and general health in the married patient group, vitality, mental, social and emotional health were found to be higher for married patients than for those of single patients (p<0.05) (Table 4). One unexpected result was that the mean scores in the SF-36 Quality of Life Scale sub-dimensions for those with chronic diseases (n=92) and those with no disease (n=28) were close to each other (p<0.05).

DISCUSSION

The relationship between obesity and chronic diseases is complex. In addition to the genetic, hormonal and neurogenic effects of obesity, it is thought that it also causes the release of pro-inflammatory cytokines. Obesity makes controlling symptoms difficult in the presence of chronic diseases, and also results in more frequent hospitalizations and a lower quality of life.[2-5] There is an association between improvements in obesity-related comorbidities and an increase in HRQL.[8] It is also known that patients prefer surgical treatment due to the deterioration of their quality of life caused by obesity.[10,16] Clinical markers cannot always be decisive when evaluating the results of health interventions. Sometimes, results known only by the patient can only be understood through their direct responses. Satisfaction with the intervention and general happiness indicates an improvement in the patient's quality of life and this can be a sufficiently valid reason for this intervention.[17]

In this study, a remarkable finding is that although the patients were relatively young on average, 76.7% of them had at least one health complaint which harmed their quality of life and they used drugs to treat it. Adults with metabolic disease prefer BS because they think they can live longer. Syn et al.[18] found in their study that the survival benefit of BS was more pronounced in those with pre-operative diabetes than in those without. In our study, those individuals with a low mean age

Table 4. Scores of the patients from the SF-36 Quality of Life Scale sub-dimensions according to some descriptive characteristics

Introductory features	Physical function (mean ± SD)	Physical role (mean ± SD)	Emotional role (mean ± SD)	Energy/ vitality (mean ± SD)	Mental health (mean ± SD)	Social function (mean ± SD)	Pain (mean ± SD)	General perception of health (mean ± SD)
Age								
18-25	100	100	66	65	40	50	87.5	40
26-35	94.70	100	82.00	71.47	66.11	80.14	88.08	94.41
36-45	96.25	100	90.79	70.62	77.00	85.93	94.68	88.50
46-55	100	100	100	85.71	90.85	100	100	91.66
56 and over	86.66	100	96.22	81.66	81.33	87.50	89.16	83.57
Gender								
Female	93.21	100	87.85	69.64	69.90	80.35	90.35	86.28
Male	99.16	100	91.50	84.16	84.66	93.75	96.66	90.83
Education								
Primary education	86.36	100	96.90	72.27	76.00	89.77	80.90	95.45
High school	98.12	100	87.25	66.56	78.75	81.25	100	89.62
University	96.36	100	87.12	78.18	71.63	84.09	92.27	84.09
Marital status								
Married	95.66	100	92.06	78.00	75.91	88.33	90.33	87.33
Single	93.00	100	79.60	62.00	69.60	72.50	98.00	88.60
Chronic disease								
Yes	95.76	100	90.02	77.60	76.69	85.59	92.01	85.67
No	92.50	100	85.42	62.14	66.57	80.35	93.03	94.14

SF-36: 36-Item Short-Form Survey, SD: standard deviation.

and high comorbidity had a long-life expectancy and decided to have BS. Statistically significant improvement was noted in their diseases and drug use after surgery and in their weight loss (p=0.011). A high level of quality of life after bariatric surgery is an important indicator of the success of this operation. We consider it a limiting feature of our study that we did not perform a pre-operative quality of life appraisal and a post-operative comparison group.

The results of this study showed that overall HRQL was high one year after bariatric surgery. The mean value of quality of life was found to be high and statistically significant in terms of physical function, perception of pain, physical role, perception of general health, vitality, mental role, social function and mental health (Table 3). The improvement in physical function, physical role and pain perception was found to be significantly higher than the other life perception sub-dimensions. This results appear to be consistent with other research in this area. SF-36 is the most frequently used HRQL measurement in bariatric surgery studies and a 2020 review by Coulman and Blazeby[19] showed that the physical components of HRQL developed more easily than the mental components. The largest improvements in HRQL occurred 1-2 years after surgery. Previously published studies have found that bariatric surgery is effective in improving overall quality of life and is more efficient in restoring physical quality of life than the other specific areas of quality of life measured. In their multicenter studies, Amichaud et al.[20] reported that bariatric surgery offered a significant improvement in the short-term quality of life. Takemoto et al.[21] reported significant progress in both mental and physical features of QoL one year subsequent to bariatric operations and that they remained stable for the next 5 years. Santos et al.[22] obtained health data from 84 people who had had bariatric surgery 5 years previously through questionnaires and telephone interviews. They found that weight loss continued over the first 2 years. Afterwards, they saw that weight increased and quality of life decreased inversely in those with less physical activity.[22] People with BS need to avoid having a sedentary life for permanent weight loss. Pokorski and Głuch[23] observed that mental health and general quality of life improved after laparoscopic sleeve gastrectomy in 52 obese patients and recommended surgery in their study. Poelemeijer et al.[24] reported major improvements 1-year post-bariatric surgery and that there was no difference between the surgical mode except for physical function and general health perception. The aforementioned results were found to be compatible with our study.

An interesting result in the demographic distribution of this study was that bariatric surgery was preferred more on females, married people and university graduates. In terms of age distribution, it was most preferred by individuals between 25 and 46 years old.

In this study, patients with chronic disease were more than those without chronic disease. In cases with comorbidity, this operation is riskier and less improvement in HRQL is expected. However, in the study, it was observed that those patients with chronic diseases had similar quality of life sub-dimension score averages to those without chronic diseases over the short time of 1 year ($p<0.05$).

In this study, the patients' physical quality of life was higher than their mental quality of life. There are some results from other studies which align with our study. Sierżantowicz et al.[25] found that bariatric treatment provided long-term benefits, especially in the physical component score while the psychological response was lower. This was interpreted as indicating that the patients' weight loss and physical recovery had faster clinical repercussions. However, it was thought that mental health and mental quality of life deteriorations were more difficult to recover from and this would take time or clinical support should be sought in this direction.

It is expected that this operation is riskier in cases of comorbidity. It is a striking result that the physical health of these patients with chronic diseases in this study improved after the short period of one year. It was determined that the mean physical role scores of those patients with chronic diseases were not statistically different from those without any chronic disease.

In summary, this results indicate that the mean HRQL score in the early period was high in the group of patients who had undergone bariatric surgery for the treatment of obesity. Obesity-related chronic disease complaints and the number of drugs used for these diseases have also decreased. Therefore, bariatric surgery is a useful intervention especially for obese patients with respiratory distress who cannot lose weight via conservative methods. It should be supported by clinical follow-up in order to maintain these effects in the long term.

CONCLUSION

Available data suggest that obese patients may benefit from bariatric surgery in terms of disease control, medication use and quality of life. These benefits have been gained with weight loss. To recommend bariatric surgery, it is important to determine the reasons for not losing weight via standard methods. Patients should be followed up to avoid any long-term risks of bariatric surgery complications or weight regain.

MAIN POINTS

- Obesity is a different disease with heterogeneous characteristics and its treatment is complex. The treatment of many comorbid diseases is thought to be related to the treatment of obesity.
- An increased tendency for BS has been observed recently in the obese population. The young mean age of the patient population of this study supports this view.
- The patient population of this study appeared to have a young mean age. This may be related to the patients' decision to live a healthy life via surgery. Although the patient population was young, it was observed that most of them had at least one comorbid disease.
- Obese patients could benefit from bariatric surgery in terms of weight-related disease control, medication use and quality of life.
- Patients should be followed up to avoid any long-term risks of bariatric surgery complications or weight regain.

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ETHICS

Ethics Committee Approval: The necessary permission for this study was obtained from the Near East University Clinical Research Ethics Committee (approval number: YDU/2020/81-1133, date: 30.07.2020).

Informed Consent: After the patients were informed about this study, verbal consent was obtained from those who volunteered to participate.

Peer-review: Externally and internally peer-reviewed.

DISCLOSURES

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RESEARCH ARTICLE

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Investigation of Total Antioxidant Status and Total Oxidant Status with Seizure Types in Patients with Epilepsy

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Abstract

BACKGROUND/AIMS: As epilepsy is a complex disease group, it is difficult to diagnose and classify. Oxidative stress plays a vital role in the pathogenesis of epilepsy. This study investigated the total oxidant/antioxidant status levels in patients with focal onset and generalized onset seizures. The results we obtained may help find the etiological cause in patients with seizure complaints and may guide their treatment. In addition, knowing the seizure type of the patient can give an idea about the prognosis of their disease.

MATERIALS AND METHODS: The total number of patients included in this prospective study was 58. There were also 57 people in a control group. The patients were classified according to their type of seizure: focal or generalized onset. The serum oxidative stress index (OSI) and total oxidant/antioxidant status values of all patients and control group members were measured. The patients (focal/generalized groups) and control group members were compared.

RESULTS: This prospective study was completed with 58 eligible patients who met the inclusion criteria. There were 57 people in the control group. Total oxidant status (TOS) and OSI levels were higher in the seizure groups compared to the control group ($p<0.05$). The difference between the serum TOS and OSI levels of patients with generalized or focal onset seizures was statistically significant.

CONCLUSION: Classifying patients according to their seizure types by looking at their oxidative stress levels can guide treatment (in terms of investigating antioxidant activity) and give an idea about prognosis. This study showed the importance of TOS and OSI levels in patients presenting with seizures. This was particularly evident in generalized onset seizures. An evaluation of serum TOS and OSI levels in patients presenting with seizures may help us in clinical diagnosis, treatment, and classification.

Keywords: Epilepsy, total oxidant status, seizure types, total antioxidant status

INTRODUCTION

Epilepsy is a common disorder characterized by seizures. It affects people of all ages. Anamnesis, neurological examinations, neuroimaging, and electroencephalography (EEG) examinations are essential in diagnosis. Since epilepsy is a complex disease group, it is difficult to diagnose and classify. Classification is necessary for the prognosis and treatment of this disease. According to the seizure types, epilepsies were determined by the International League Against Epilepsy (ILAE) in 2017; seizures were classified as focal onset, generalized onset, and seizures of unknown origin.[1,2]

The presence of oxidative stress has been shown in the pathogenesis of this disease.[3,4] Studies have shown that oxidative stress levels are higher in epilepsy patients than in healthy individuals.[5,6] Structural changes resulting from oxidative stress appear as an increased risk of seizures or

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recurrent seizures.[7] Total antioxidant status (TAS), a marker of oxidative stress, and total oxidant status (TOS) have been defined in recent years. The presence of high TOS and oxidative stress index (OSI) and low TAS levels in epilepsy patients have been shown in studies.[8,9]

Studies on epileptogenesis are noteworthy. This study investigated the levels of oxidative stress markers (TOS, TAS, OSI) in patients with focal and generalized onset seizures. We hope that the results we obtained will contribute to the classification of patients with seizure complaints. This may be particularly beneficial for patients in the group whose seizure type cannot be classified. In addition, knowing the seizure type of the patients can give an idea about the prognosis of the disease and can guide antioxidant treatment strategies.

MATERIALS AND METHODS

This study was conducted in the Emergency Medicine and Clinical Biochemistry departments. Bezmialem Vakıf University Ethics Committee approval (approval number: 2021/177, date 29.04.2021) was obtained for this study. The research was completed in accordance with the criteria specified in the Declaration of Helsinki. The number of patients included in this study was 58. The study was completed by forming a control group of 57 healthy individuals. Informed consent was obtained from the patients with epilepsy (or their primary relatives) and those in the control group. All patients were diagnosed with epilepsy according to the ILAE diagnostic criteria by evaluating their clinical symptomology, EEGs, and imaging findings. The age, gender, seizure type, body mass index, and clinical characteristics of the people included in this study were recorded. Patients were classified according to their type of seizure: either focal or generalized onset.

According to the results of the EEG, they were grouped into those with or without epileptogenic findings. Those whose seizure type was not determined (seizures that could not be classified according to ILAE 2017 seizure classification), without EEG, those with chronic systemic diseases, those using immunosuppressive drugs, pregnant women, substance abusers, chronic drug users (excluding anti-epileptics), those under the age of 18 years, and those who did not give consent were excluded from this study (Figure 1). The physical and neurological examinations of the control group were normal. They had similar age and gender characteristics to the patient group. The blood TOS, TAS, and OSI values of all patients and control group individuals were measured. Serum samples were obtained from those patients with epilepsy who visited the emergency department with seizures, during or immediately after a seizure, within the first hour for patients who had seizures at home and at any time in the healthy controls. Venous blood samples of 10 cc were taken from the seizure and control groups, centrifuged at 5,000 rpm for 10 minutes, and stored at -80 ºC. Biochemical measurements were made at the Clinical Biochemistry Laboratory of our hospital.

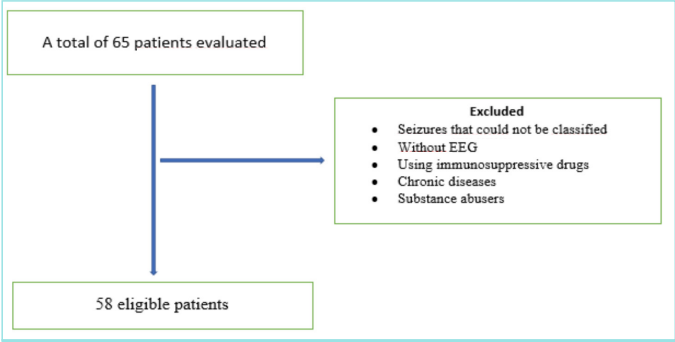

Figure 1. Patient flow diagram for inclusion in this study.
EEG: electroencephalography.

The OSI, TAS and TOS values of the patient (focal and generalized) and control groups were compared. The laboratory parameters and EEG findings of the epileptogenic and non-epileptogenic patient groups were statistically compared.

Measurement of the TOS: A method developed by Erel[10] was used to measure the TAS level of the serum. In this method, hydroxyl radical is formed by using the iron solution and hydrogen peroxide. Thus, the anti-oxidative effect against free radical reactions is measured.[10]

Measurement of TAS: The TAS level was measured via the colorimetric method developed by Erel[10]. He used the hydroxyl radical in this method. Oxidative reactions initiated by the addition of a plasma sample provide an effective measure of the plasma TAS level.[11]

Determination of OSI: The formula used for the OSI value is OSI = TOS (mmol)/TAS (mmol).[12]

Statistical Analysis

Quantitative variables were determined using centralization and measures of variance (mean ± standard deviation). The Kruskal-Wallis and the Mann-Whitney U tests were used in cases where the assumptions of normality and homogeneity were not met to show behavioral differences of the group averages. A value of $p=0.05$ or below was determined to be statistically significant. Statistical analyses were carried out with the IBM Statistics Package for Social Sciences for Windows program. According to an ANOVA test, the required sample size was 58 for the effect size - Cohen's $(f)=0.4$ and power $(1-\beta)=0.80$ at ($\alpha=0.05$ statistical significance).

RESULTS

This study was completed with 58 eligible patients who met the inclusion criteria. It was a prospective study. There were thirty males (51.7%) and 28 females (48.3%) in the patient group with a mean age was 43.5±19.3 years. The control group had 57 people. There was no significant demographic difference between the seizure and control groups. The clinical features of the control and epilepsy groups are shown in Table 1. An EEG examination of all patients was performed. Epileptogenic activity was found in 16 (27.6%) patients. Computed tomography was performed in 21 (36.2%) patients. Thirty-seven (63.8%) patients were using a single anti-epileptic, thirteen (22.4%) used multiple anti-epileptics, and eight (13.8%) were not using any anti-epileptics. There were 42 patients with generalized onset seizures (36.5%), 16 with focal onset seizures (13.9%), and a control group which consisted of 57 subjects (49.6%). The routine laboratory results obtained from the patients are given in Table 1.

The TOS and OSI levels were significantly higher in the seizure group compared with the control group (Table 1) ($p<0.05$). In the serum taken from the patients, the TOS level was 32.44±23.78, and the OSI level was 4.67±3.81. When the TAS levels were examined, no statistically significant difference was found between the seizure and control groups. (TAS=0.71±0.19). There was a statistically significant difference between the serum TOS and OSI levels in the generalized

Table 1. The clinical and laboratory features of the control and seizure groups

		Seizure (n=58) (mean ± SD)	Control (n=57) (mean ± SD)	p-value
Age	Years	43.59±19.33	43.15±9.24	0.617
Gender	Female	28 (48.3%)	28 (49.1%)	0.908
	Male	30 (51.7%)	29 (50.8%)	
BMI	Kg/m^2	25.76±2.65	26.89±2.44	0.377
TAS	mmolTrolox Eq/L	0.71±0.19	0.74±0.09	0.574
TOS	µmol H_2O_2 Eq/L	32.44±23.78	3.78±4.13	<0.05
OSI	Arbitrary unit	4.67±3.81	0.54±0.58	<0.05
Antiepileptic	Single	37 (63.8%)	-	-
	Two or more	13 (22.4%)	-	-
	Not using	8 (13.8%)	-	-
Seizure types	Generalized	42 (36.5%)	-	-
	Focal	16 (13.9%)	-	-
WBC	$10^{\wedge}3/\mu L$	11.05±4.65	8.35±2.05	<0.05
Hemoglobin	g/dl	13.43±2.35	13.62±1.95	0.690
Platelet	$10^{\wedge}3/\mu L$	267.64±88.09	275.67±89.62	0.554
Sodium	mmol/L	137.71±3.93	135.65±4.15	0.060
Potassium	mmol/L	4.09±0.47	3.6±0.62	0.529
Calcium	mg/dL	9.38±0.53	8.76±0.75	0.316
BUN	mg/dL	14.48±6.64	12.8±1.6	0.334
Creatine	mg/dL	0.89±0.48	0.95±0.24	0.790
AST	U/L	27.76±23.45	31.77±17.46	0.433
ALT	U/L	24.55±14.25	29.98±16.51	0.352
Albumin	g/L	3.8±0.53	3.76±0.75	0.252

TAS: total antioxidant status, TOS: total oxidant status, OSI: oxidative stress index, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, BMI: body mass index.

onset and focal onset patient groups (p^1<0.05) (Table 2). Likewise, there was a statistically significant difference between the serum TOS and OSI values of patients with generalized onset seizures and the control group (p^3<0.05) (Table 2). There was no significant difference between the focal onset seizure patients and the control group in terms of TAS, TOS, and OSI levels (p^2>0.05) (Table 2). No statistically significant difference was found between the serum TOS, TAS, and OSI levels obtained from those patients with normal and epileptiform activity in the EEG (Table 3).

DISCUSSION

The presence of high oxidative stress levels and low antioxidant status in patients with epilepsy has been shown in many studies.[13-15] This study evaluated the relationship between oxidative stress biomarkers (TAS, TOS, and OSI) and seizure types in patients with epilepsy. TOS and OSI levels were higher in the group with epileptic seizures. The difference between them was statistically significant when compared with the control group. At the same time, TAS levels were lower in the epilepsy groups compared with the control group (Table 1). This result suggests that low antioxidant levels contribute to the epileptogenesis process. The brain has a high oxidative metabolism, and when antioxidant capacity decreases, seizures can be seen through neuronal hyper-excitability.[16,17] In fact, the deterioration of the oxidant/antioxidant balance, which occurs with a decrease in antioxidant enzyme activities, may pave the way for generalized seizures.[18]

In this study, serum TOS and OSI levels were significantly higher in the generalized onset seizure group compared with both the focal and control groups (Table 2: p^1, p^3). The difference between serum TAS, TOS and OSI levels measured in the focal-onset group and the control group was not statistically significant (Table 2: p^2). Focal seizures are caused by abnormal electrical activity originating in an area of our brain.[19,20] Can it be said that focal seizures do not affect the oxidative balance

Table 2. The TOS, TAS and OSI levels in focal, generalized and control group

	Seizure types (mean ± SD)		Control (57) (mean ± SD)	p-value*		
	Focal (n=16)	Generalized (n=42)		p^1	p^2	p^3
OSI	3.43±3.07	5.14±3.99	0.54±0.58	**<0.05**	0.277	**<0.05**
TAS	0.68±0.22	0.72±0.18	0.74±0.09	0.898	0.574	1
TOS	22.91±17.03	36.07±25.13	3.78±4.13	**<0.05**	0.358	**<0.05**

p^1: focal/generalized, p^2: focal/control, p^3: generalized/control, *Kruskal-Wallis test, SD: standard deviation, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index.

Table 3. TOS, TAS, and OSI levels obtained from patients with activity in the EEG

	Electroencephalography		p-value*
	Epileptogenic (n=16) (mean ± SD)	Normal (n=42) (mean ± SD)	
OSI	5.32±4.68	4.42±3.46	0.645
TAS	0.69±0.22	0.71±0.18	0.709
TOS	34.0±25.79	31.85±23.28	0.830

*Mann-Whitney U test, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, EEG: electroencephalography, SD: standard deviation.

significantly? In our study, it was revealed that the use of biomarkers, such as TAS, TOS, and OSI, might not be useful in focal-onset seizures.

Whether high TOS is a cause, or a consequence of seizures should be further investigated. If it is the cause of seizures, we can conclude that high TOS and OSI levels may trigger a generalized seizure. If it is the result of seizures, we can say that focal seizures (because they remain more localized) do not increase TOS and OSI levels as much as generalized seizures. In the classification of seizure types made by the ILAE in 2017, patients whose seizure type could not be determined were included in the "unknown seizures" group.[21,22] However, the classification of epilepsy patients according to seizure type is clinically valuable because such classifications guide treatment and can give us an idea about the prognosis of the disease.[23,24] In epilepsy, the distinction between focal and general seizures should be made whenever possible. This information is important in deciding which treatment plan is more effective. Some drugs of choice for treatment (e.g., carbamazepine and lamotrigine) are often used to treat focal seizures, while others (e.g., sodium valproate) are usually used for generalized tonic-clonic seizures. TAS, TOS, and OSI levels can help determine the type of seizure.

It should be investigated whether it is possible to classify seizures of unknown onsets by looking at the serum TAS and TOS levels of the patients. Knowing and recognizing EEG findings is also important in the early diagnosis of diseases, in selecting appropriate antiepileptic drugs, and in evaluating the response to treatment.[25] Therefore, our study evaluated the TAS, TOS, and OSI levels of patients with typical EEG findings and patients whose EEG was considered normal, but we observed no statistically significant difference. About half of all EEGs for patients who have already had seizures are interpreted as normal.[26] EEG detects interictal epileptiform discharges in about 50% of patients with epilepsy.[27] In our study, no relationship was shown between EEG results and oxidative stress markers, but using video EEG in future studies may be illuminating in this regard.

The seizure group had higher white blood cell levels than the control group, which may be a result of muscle activity during seizures. Many studies support this result.[28] Renal and hepatic function tests (urea, creatinine, aspartate aminotransferase, alanine aminotransferase, an albumin) were within normal limits in all patients (Table 1). Even if laboratory parameters do not have a place in the diagnosis of epileptic seizures, they can be a guide for etiology and treatment (e.g. electrolyte imbalances can manifest with seizures). It is reasonable to check the hemogram, blood urea nitrogen, creatinine, electrolyte, and liver panel.

Study Limitations

Our study was limited by its small sample size. This study's limitations were the absence of video EEG and the fact that some seizures were experienced at home and could not be monitored by clinicians.

CONCLUSION

Classifying patients according to seizure types by looking at their oxidative stress levels can guide treatment (in terms of investigating antioxidant activity) and give an idea about prognosis. This study showed the importance of TOS and OSI levels in patients presenting with seizures. This was particularly evident in generalized onset seizures. An evaluation of serum TOS and OSI levels in patients presenting with seizures may help in the clinical diagnosis, treatment, and classification of epilepsy.

MAIN POINTS

- Since epilepsy is a complex disease group, it is difficult to diagnose and classify.
- This study evaluated the relationship between oxidative stress biomarkers and seizure types in patients with epilepsy.
- Serum TOS and OSI levels were significantly higher in the generalized onset seizure group compared with both the focal group and the control group.
- Evaluating serum TOS and OSI levels in patients presenting with seizures may help in the clinical diagnosis, treatment, and classification of epilepsy.

ETHICS

Ethics Committee Approval: Bezmialem Vakıf University Ethics Committee approval (approval number: 2021/177, date 29.04.2021) was obtained for this study.

Informed Consent: Informed consent was obtained from the patients with epilepsy (or their primary relatives) and those in the control group.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.T., F.U., E.S., Ş.S., Design: B.T., F.U., E.S., Ş.S., Data Collection and/or Processing: B.T., F.U., E.S., Ş.S., Analysis and/or Interpretation: B.T., F.U., E.S., Ş.S., Literature Search: B.T., F.U., E.S., Ş.S., Writing: B.T., F.U., E.S., Ş.S., Critical Review: B.T., F.U., E.S., Ş.S.

DISCLOSURES

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

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RESEARCH ARTICLE

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The Impact of Foot Reflexology on Nausea-Vomiting and Sleep Quality for Lung Cancer Patients Receiving Chemotherapy in Turkey

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**This study was presented as an oral presentation in the 1st International Congress of Internal Medicine Nursing, 25-27 November, 2018, Lara/Antalya, Turkey.

Abstract

BACKGROUND/AIMS: The aim of this study was to determine the impact of foot reflexology on nausea-vomiting and sleep quality in patients with lung cancer receiving chemotherapy in Turkey.

MATERIALS AND METHODS: This study was conducted with a pre-test/post-test experimental design. 60 patients (30 experimental group and 30 control group) receiving chemotherapy in an oncology center were included. Patients in the experimental and control groups were selected from the population using a random sampling method. Foot reflexology was given to the experimental group. After receiving the second course of chemotherapy, foot reflexology was applied for the first time to the patients in the experimental group, twice a week for four weeks; 8 sessions in total. The "Rhodes Nausea, Vomiting and Regurgitation Scale" and the "PSQI" were used in the questionnaire, which was administered to all patients twice, after receiving the second course of chemotherapy and 4 weeks later. Chi-square, Mann-Whitney U test, the Wilcoxon test and Kruskal-Wallis analysis of variance were used.

RESULTS: The sociodemographic characteristics of the patients were as follows: 53.3% of the patients in the experimental group were 61 years or older, 80% were male, 83.3% were married. 60% of the patients in the control group were 61 years or older, 86.7% were male, 83.3% were married. Most had been diagnosed less than 6 months previously (control group 63.4%, experimental group 60.0%). Most participants had first stage lung cancer (control group 80.0%, experimental group 70.0%). It was found that there was a significant difference between the control and experimental groups in terms of their nausea-vomiting and retching mean scores of "symptom experience" (p=0.0001), "symptom formation" (p=0.0001), "symptom distress" (p=0.0001), "subjective sleep quality" (p=0.0001), "sleep latency" (p=0.019), "daytime dysfunction" (p=0.002), "sleep disturbances" (p=0.002) and their means of the PSQI (p=0.002).

CONCLUSION: Foot reflexology was found to be an effective method in reducing sleep problems together with the experience, formation and distress of nausea and vomiting for those patients with lung cancer who were receiving chemotherapy.

Keywords: Chemotherapy, lung cancer, nursing, foot reflexology

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INTRODUCTION

Lung cancer accounts for about one third (19.4%) of all cancer deaths and is the most common cancer globally.[1] Lung cancer is a type of cancer which is seen in 59.3/100,000 in males in Turkey, and its mortality rate is 30.13/100,000.[2] In lung cancer, chemotherapy is used to slow the development of cancer, to prevent its spread, and to treat and alleviate its symptoms. However, cancer and chemotherapy cause many unwanted symptoms such as nausea-vomiting, anorexia, stomatitis, diarrhea, fatigue and sleep problems. These symptoms may develop within the first few days especially after chemotherapy or a few months or years later.[3,4]

Nausea-vomiting is one of the most common symptoms for those patients who receive chemotherapy for lung cancer.[5] Chemotherapeutic agents with moderate to high emetogenic risk are frequently used in the treatment of lung cancer. Despite advances in antiemetic therapies used in the prevention and control of nausea and vomiting due to cancer and chemotherapy, it was found that almost 50% of patients who suffer from cancer tend to experience acute, delayed or expected nausea and vomiting. Furthermore, even in very effective antiemetics such as serotonin antagonists, 38-80% of patients experience nausea and vomiting in a severe way and this causes 20% of patients to postpone or refuse treatment.[6,7] Uncontrollable nausea and vomiting lead to dehydration, hypotension, loss of appetite and/or weight loss due to the absorption and excretion of the drugs used in this treatment. In addition, the frequency, duration and severity of nausea and vomiting during the day disrupt the social life of these patients, increase their fear and anxiety, create difficulties in performing their daily activities and significantly reduce their quality of life.[8-10]

Having trouble with sleeping is also one of the most common symptoms of lung cancer patients. Their sleep quality usually decreases when nausea, vomiting, anxiety, pain, shortness of breath and cough are added to their already difficult situation.[8,9,11] It was found that sleep efficiency was impaired in patients who were suffering from lung cancer and receiving chemotherapy, and the amount of sleepless time during the day and night increased.[12] Patients who do not sleep enough or those with deteriorated sleep quality experience physical, cognitive and affective depression, and their feelings, thoughts and motivations suffer. Sleep problems also lead to problems such as fatigue, loss of attention, pain, irritability and hallucinations and may cause life-threatening accidents and discrepancies at work or in everyday life.[12,13] Also, sleep problems cause abnormal cortisol synthesis and modify cytokine expression and decrease the number and activity of natural killer cells with immune system functions.[5,14] This situation causes the development of infections, worsens prognosis, and increases mortality, especially in cancer patients.[15,16]

Today, reflexology applications which are applied to reduce/prevent nausea, vomiting and sleep problems in cancer patients are noteworthy.[17-19] Reflexology is "a technique that helps the normalization of body functions by a hand application to the reflex points on the hands, feet and ears associated with all of the glands, organs and body parts." In addition, reflexology is a "special pressure technique and energy balancing system". It is applied to the reflex points by applying pressure by rubbing and squeezing movements.[20-22] It is reported that reflexology, which is increasingly used in the field of health, creates a strong therapeutic effect between the patient and the nurse, reduces pain, facilitates adaptation to the disease and increases the power of adaptation and it has been reported to reduce the nausea-vomiting of cancer patients and improve their quality of life.[22,23]

Foot reflexology is often preferred due to the proximity of the pressure points to the skin surface in the feet.[24] In this application, the blocked energy is dissolved in certain parts of the body with special scrubbing movements applied to the feet and this energy is disseminated to every living tissue and every cell and the self-healing power of the body is activated.[24-26] Crystalline waste materials such as calcium and uric acid are eliminated by blood and lymphatic circulation with this application and so comfort and relaxation are provided. It has been stated that symptoms of nausea and vomiting decreased after foot reflexology applications in breast cancer patients with stage I-III disease despite antiemetic treatment.[23-28] In addition, it has been determined that the foot reflexology application can be used as a support in alleviating sleep problems in breast, stomach, liver, and ovarian cancer patients as well as cancer patients of unknown origin, increasing their sleep satisfaction, eliminating fatigue and promoting quality sleep.[20,21,27-30]

Results based on the previous literature demonstrate that foot reflexology is an effective complementary therapy method in the management of symptoms, improving physical and spiritual well-being, and improving the quality of life in cancer patients.[31,32] In this context, this paper explains the effects of the foot reflexology applications on nausea, vomiting and sleep quality in lung cancer patients receiving chemotherapy. This nursing study provides evidence of the benefits of foot reflexology on nausea-vomiting and the sleep quality of lung cancer patients.

Study Hypothesis

1. H_1: There is a difference between the experimental and control groups in terms of the effect of the foot reflexology application on the experience, occurrence and distress of nausea and vomiting symptoms in lung cancer patients receiving chemotherapy.

2. H_1: There is a difference between the experimental and control groups in terms of the effect of foot reflexology on sleep quality in lung cancer patients receiving chemotherapy.

MATERIALS AND METHODS

Study Design

This study was conducted with a pre-test/post-test experimental design.

Participants Setting and Subjects

The participants of this study were lung cancer patients in the oncology center of a university hospital in the northeast of Turkey. The size of the sample was determined using the OpenEpi program. Statistical analysis was performed with a confidence interval of 95% and a power analysis of 80%. It was planned to include 34 patients in the experimental group and 34 in the control group. However, 8 patients were withdrawn from the study; 2 died, 2 had problems with transportation, and 4 were transferred to another oncology center. Therefore, the study was conducted with 60 patients with lung cancer who were receiving chemotherapy in the oncology center of a university hospital and diagnosed with stage 1 to stage 3 cancer.

The criteria required for participation were as follows: being 18 years of age or over, being conscious, being able to speak Turkish, receiving their second chemotherapy treatment, having a life expectancy of longer than six months, knowing their cancer diagnosis, being patients who had received chemotherapy agents whose emetogenic risk was either moderate (Doxorubicin, Mitoxantrone, etc.), high (Methotrexatea, Cisplatin, etc.) or very high (Cisplatin Dacarbazine etc.), those who were experiencing sleep problems, who did not have a diagnosis of any psychiatric disorder, who did not have any foot impediments (open wound, fracture or infection on the foot), who stated that they had experienced symptoms of nausea-vomiting and sleep problems after their first course of chemotherapy and who agreed to participate in this study. The participants were divided into experimental (n=30) and control (n=30) groups. It took four weeks to complete the study process for both groups. The patients in the experimental and control groups were selected from the population using a random sampling method.

Data Collection Tools

The "Patient Information Form", "Rhodes Scale of Nausea-Vomiting and Retching (RINVR)" and the "Pittsburgh Sleep Quality Scale (PSQI)" were used as the data collection tools.

Patient information form: The patient information form, which was created by the researcher as a result of a literature review[25,33-35] consisted of two parts, with 14 questions in total. Seven questions in the first part evaluated the sociodemographic characteristics (age, gender, marital status, education level, place of residence, occupation, and monthly income level) of the patients. Seven questions in the second part were included to determine the disease variables (diagnosis period, cancer stage, disease, nausea and vomiting and sleep problems, knowledge of the effects and side effects of chemotherapy, and the presence of any other chronic diseases).

Rhodes Scale of Nausea-Vomiting and Retching: RINVR was developed by Rhodes and McDaniel,[36] and its validity and reliability tests were again carried out by Rhodes and McDaniel,[36] Items 1, 3, 6 and 7 are reverse-rated. For each response, minimum distress is scored as 0 and maximum distress is scored as 4. The patient's experience of nausea and vomiting in each of the eight items is collected. The highest possible result is 32 and this indicates the most severe symptom formation score. The Cronbach alpha of the RINVR is 0.98.[36] The adaptation of this scale to the Turkish population was conducted by Genc[25] The Cronbach alpha internal consistency coefficient of this scale was found to be 0.95. The Cronbach alpha internal consistency coefficient of the RINVR for this study was found to be 0.92.

Pittsburgh Sleep Quality Scale: It was developed in 1989 by Buysse et al.[37] to evaluate sleep quality in psychiatric practice and clinical trials. The PSQI assesses sleep quality over the past month. Nineteen of the 24 questions that PSQI contains are self-report. Five questions are answered by a roommate or spouse. The last five questions are used only for clinical information and are not included in the analyses. Question 19 is about whether a roommate or partner's comment is taken into account when determining the total and component scores of the PSQI. Self-reporting questions include various factors related to sleep quality. They are related to the frequency and severity of sleep duration, sleep latency and sleep-related specific problems. Eighteen items are grouped into seven components, some of which are indicated by a single item, while others are obtained by grouping several items. Each item is rated from 0 to 3 points. The sum of the seven components gives the total PSQI score. The total score has a value between 0 and 21. A high total score indicates poor sleep quality. Furthermore, if the PSQI global score is greater than five, it indicates poor sleep quality. The validity and reliability studies of this scale for our country were carried out by Yücel Ağargün et al.[38] and the Cronbach alpha reliability coefficient of the scale was found to be 0.80. The PSQI Cronbach alpha internal consistency coefficient was found to be 0.74 in this research.

Researcher's Foot Reflexology Competence: In Turkey, a certificate from a program which includes 40 hours of theoretical and practical training is required for nurses in order to be able to perform Foot Reflexology. Therefore, one of the researchers received a certificate by participating in a course conducted by the "İstanbul Reflexology-Psychology Center", which included a 40-hour theoretical and practical training program between December, 2015 and January, 2016.

Procedure

Control group: This study was first started with the control group patients. Those patients who met the research criteria and agreed to participate in this study were included. After the data of the patients in the control group were completed, the patients in the experimental group were analyzed. Control group and experimental group patients did not see each other and were not affected by each other. These participants were contacted after their second chemotherapy treatment. The "Patient Information Form", "RINVR" and "PSQI" were used. The researcher did not apply foot reflexology to the control group. "RINVR" and "PSQI" were applied again to the patients in the control group after four weeks.

Experimental group: When patients were admitted to the Oncology Center for their second chemotherapy treatment, the "Patient Information Form", "RINVR" and "PSQI" were applied. Then, the first foot reflexology application was performed on these patients during their second chemotherapy treatment. A total of eight-foot reflexology sessions were performed twice a week for a total of four weeks for the experimental group patients. The foot reflexology application was applied to both feet for a total of 30 minutes**.** Although the frequency and number of reflexology applications performed on cancer patients vary in different studies, it is recommended to perform an average of four to eight sessions of 30 minutes in order to affect the organs, ladders and other parts of the body and to open any blockages.[20,28,30,39] "RINVR" and "PSQI" were re-administered after the eighth session of reflexology for these patients.

Foot Reflexology Practice

The foot reflexology application was performed by the researcher in a special room in the oncology center. First of all, the patients were informed about the foot reflexology application. The patient's feet were placed in a way to make eye contact with the patient, and the patient's feet were placed in a sitting position with the practitioner's chest level. After lubricating the feet with olive oil, the reflexology application was started with the right foot first. Initially, five minutes of warm-up and relaxation exercises were performed on the feet. In order to send a message to the whole body, the solar plexus point

was pressed 8-10 times with the thumb. Pressure was applied to the pituitary gland and hypothalamus reflex points on the big toe with caterpillar movements for one minute, and pressure was applied to the spleen and thyroid reflex points via pressing, pulling and caterpillar movements. A friction movement was performed with the thumb on the reflex point of the adrenal glands for one minute. The reflex points relating to nausea-vomiting and sleep problems were pressed for one minute. The reflex points reflecting the intestine were pressed via the caterpillar movement using the thumb. For three minutes, compression was applied to the spinal cord reflex points in the form of a worm walk with the thumb from top to bottom. The reflex points of the uterus, vagina, ovaries and fallopian tubes were compressed for three minutes. Finally, the application was completed by pressing the solar plexus again. All applications on the right foot were repeated on the left foot. These applications took a total of 30 minutes for both feet (Figure 1).[40]

Ethics Committee Approval

Permission was obtained from the Karadeniz Teknik University Faculty of Medicine Clinical Research Ethics Committee (approval number: 24237859\291, date: 31.05.2016) in order to carry out this research. Written approval was also obtained from the institution where this study was conducted (approval number: 64960800\799, date: 31.05.2016). Informed consent forms outlining the aims and procedures of this study were obtained from all participants who were guaranteed confidentiality. This study conformed to the principles of the Declaration of Helsinki.

Statistical Analysis

The SPSS (IBM) for Windows 23.0 program was used. Descriptive data were indicated as minimum, maximum, mean, standard deviation, number and percentage. Chi-square was used for the comparison of categorical variables of the groups, and Mann-Whitney U, Wilcoxon and Kruskal-Wallis Variance Analysis tests were used to evaluate differences between continuous variables with a significance level of $p<0.05$.

RESULTS

This study included a total of sixty patients (30 control, 30 experimental) who were suffering from lung cancer. Those participants who were 61 years or older made up 53.3% of the experimental group and 60% of the control group. The majority of the participants were male (control group = 86.7%, experimental group = 80.0%;) and married (83.3%). The educational level in the 2 groups were different (53.3% of the participants in the experimental group had primary education; 36.7% of the participants in the control group were literate); 73.3% of the participants in the experimental group and 63.3% of those in the control group were employed. A significant proportion of participants in both groups were living in a village (control group = 46.7%, experimental group = 43.3%). Most had been diagnosed less than 6 months previously (control group = 63.4%, experimental group = 60.0%). Most participants had first stage lung cancer (control group = 80.0%, experimental group = 70.0%). There was found to be no significant difference between the control and experiment group in terms of their descriptive characteristics ($p>0.05$) (Table 1).

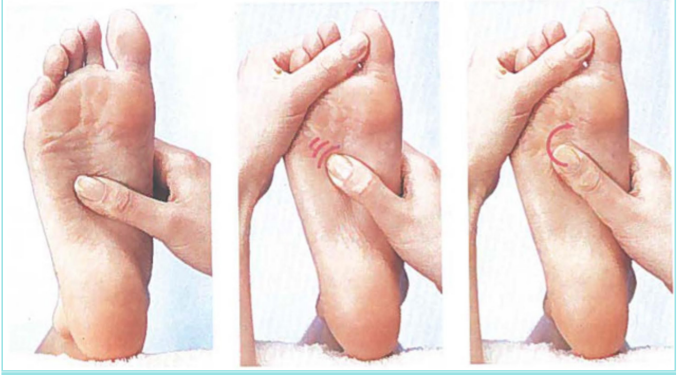

Figure 1. Some movements used in foot reflexology.[40]

The RINVR mean scores of the control group were higher than those of the experimental group, with the experimental group having better RINVR (symptom experience, symptom formation and symptom distress) mean scores for all subscales than the control group (Table 2).

There were statistically significant differences between the experimental and control groups in the RINVR symptom experience of nausea ($p=0.0001$), vomiting ($p=0.0001$), retching ($p=0.0001$), total ($p=0.0001$); symptom formation of nausea ($p=0.0001$), vomiting ($p=0.003$), retching ($p=0.0001$), total ($p=0.0001$); and symptom distress of nausea ($p=0.0001$), vomiting ($p=0.002$), retching ($p=0.0001$), total ($p=0.0001$) (Table 2).

The PSQI subscale mean scores of the experimental group was lower than those of the control group, with the experimental group having better PSQI mean scores for all subscales than the control group (Table 3).

There were statistically significant differences between the experimental and control groups in the PSQI subscales of subjective sleep quality ($p=0.0001$), sleep latency ($p=0.019$), sleep disturbances ($p=0.012$), daytime dysfunction ($p=0.002$), and PSQI total ($p=0.002$) (Table 3).

DISCUSSION

Our results showed that the experimental group had significantly better RINVR subscale mean scores than the control group in terms of symptom experience, symptom formation, and symptom distress related to nausea, vomiting and retching. Similar improvements were previously reported from foot reflexology. Yang[41] determined in a study conducted with breast cancer patients receiving cancer chemotherapy that nausea and vomiting decreased for the patients in the experimental group after a total of four sessions of foot reflexology. It was found in Özdelikara and Tan[28] study on the impact of foot reflexology on nausea, vomiting and fatigue related to cancer chemotherapy in patients with breast cancer that total score averages of nausea, vomiting and retching symptoms of the patients in the experimental group decreased and the difference after the application was found to be statistically significant between the groups. In addition, it was reported in different study that foot reflexology reduced pain, fatigue, anxiety and depression symptoms in patients receiving cancer chemotherapy and was also effective indirectly in reducing nausea and vomiting.[42] Our results are consistent with other studies in the literature showing that foot reflexology, which we performed for lung cancer patients twice a week for a total of eight sessions, relieves patients who experience nausea,

Table 1. Descriptive and disease characteristics of the patients in the experimental and control groups (n=60)

Descriptive and disease characteristics		Experimental group, n (%)	Control group, n (%)	p
Age	40-60 years	14 (46.7)	12 (40.0)	0.602[a]
	≥61 years	16 (53.3)	18 (60.0)	
Gender	Female	6 (20.0)	4 (13.3)	0.488[a]
	Male	24 (80.0)	26 (86.7)	
Marital status	Married	25 (83.3)	25 (83.3)	1.000[b]
	Single/widowed/divorced	5 (16.7)	5 (16.7)	
Education	Literate	9 (30.0)	11 (36.7)	0.384[b]
	Primary education	16 (53.3)	10 (33.3)	
	High school	4 (13.3)	6 (20.0)	
	University	1 (3.4)	3 (10.0)	
Employment	Employed	22 (73.3)	19 (63.3)	0.405[a]
	Unemployed	8 (26.7)	11 (36.7)	
Cancer duration	≤6 months	18 (60.0)	19 (63.4)	0.777[b]
	7-12 months	6 (20.0)	6 (23.3)	
	≥13 months	6 (20.0)	4 (13.3)	
Cancer stage	I. stage	21 (70.0)	24 (80.0)	0.359[b]
	II. stage	7 (23.3)	3 (10.0)	
	III. stage	2 (6.7)	3 (10.0)	
The presence of chronic disease	Yes	18 (60.0)	14 (46.7)	0.301[a]
	No	12 (40.0)	16 (53.3)	

[a]: chi-square test, [b]: Fisher's exact test.

vomiting, and retching. These results confirm that there is a difference between the experimental and control groups in terms of the effect of the foot reflexology application on the experience, occurrence and distress of nausea, vomiting and retching symptoms in lung cancer patients receiving chemotherapy.

The results of the current study also proved that the experimental group had significantly better PSQI subscales compared to the control group in terms of subjective sleep quality, sleep latency, sleep disorder, daytime dysfunction and the PSQI total mean scores. Subjective sleep quality, which is one of the PSQI subscales, shows how patients fully evaluate their sleep quality. In Turkey, it is stated that chemotherapy-related fatigue decreased and the quality of sleep increased after foot reflexology was applied to breast cancer patients.[28]

In our study, the mean sleep latency scores of the patients in the experimental group were found to be significantly lower and this means that these patients fell asleep in a shorter time. In other words, our reflexology practice relieved the experimental group patients and made it easier for them to fall asleep. In the study of Demiralp et al.[43], relaxation exercises were applied to cancer patients receiving chemotherapy and it was found that patients in the experimental group had lower sleep latency mean scores after exercise.

In different studies, it was stated that physical problems such as dyspnea, pain, fever and cough caused sleep disorders in cancer patients.[44-46] In our study, the patients in the experimental group experienced less sleep disorders after foot reflexology. Sleep disorders include waking up at midnight or early in the morning, waking up to go to the toilet, uncomfortable breathing, coughing during sleep, excessive feelings of warmth and feelings of heat, nightmares and pain during sleep. In the literature, it is stated that the foot reflexology application improves sleep quality by reducing levels of fatigue and pain in cancer patients.[29,47]

Daytime dysfunction shows how often patients force themselves to stay awake during a ride, a meal, or during a social activity and the extent to which day-to-day work is problematic to do. In our study, the experimental group patients had less difficulty in performing daytime functions. Le GuenY et al.[48] found that sleep efficiency was impaired in lung cancer patients and the amount of sleepless time during the day and night increased.

In our study, the mean PSQI total score of the experimental group patients decreased significantly and they had better sleep quality after the foot reflexology application. In parallel with our study, Park et al.[49] reported that sleep quality was improved and pain sensation decreased in breast cancer patients after foot reflexology. Nazik et al.[50] applied progressive relaxation techniques to cancer patients who were receiving chemotherapy and found the mean PSQI pre-test score in the experimental group to be 11.70±1.87, the final test score was 4.93±2.13, and the difference between the groups was significant. These results supported the idea that "there is a difference between the experimental and control groups in terms of the effect of foot reflexology on sleep quality in lung cancer patients receiving chemotherapy". In line with our current study and the literature, it can be concluded that foot reflexology can be safely applied to lung cancer patients by nurses/doctors or reflexologists who are trained in the relevant field.

Table 2. The comparison of the subscales measures of RINVR in the experiment and control group patients after the foot reflexology application

RINVR* sub-scales			Before reflexology	After reflexology	p**
			Mean ± SD	Mean ± SD	
Symptom experience	Nausea	Experimental	7.1±3.12	3.5±1.81	0.0001[a,γ]
		Control	5.7±3.40	7.6 ±3.30	0.003[b,γ]
		p***	0.1[δ]	0.0001[a,δ]	-
	Vomiting	Experimental	3.9±2.26	2.1±1.83	0.0001[a,γ]
		Control	3.1±3.24	4.9±3.52	0.006[b,γ]
		p***	0.073[δ]	0.0001[a,δ]	-
	Retching	Experimental	4.5±2.39	2.2±1.20	0.0001[a,γ]
		Control	4.3±2.33	4.6±2.50	0.217[γ]
		p***	0.604[δ]	0.0001[a,δ]	-
	Total	Experimental	15.5±6.63	7.9±3.93	0.0001[a,γ]
		Control	13.0±7.43	17.2±7.98	0.001[b,γ]
		p***	0.123[δ]	0.0001[a,δ]	-
Symptom formation	Nausea	Experimental	4.9±2.16	2.3±1.27	0.0001[a,γ]
		Control	4.2±2.40	5.0±1.96	0.026[b,γ]
		p***	0.195[δ]	0.0001[a,δ]	-
	Vomiting	Experimental	1.9±1.77	0.7±1.09	0.001[b,γ]
		Control	4.2±2.40 (1.7±2.39)	2.7±2.74	0.065[γ]
		p***	0.372[δ]	0.0001[a,δ]	-
	Retching	Experimental	2.4±1.13	2.2±1.20	0.539[γ]
		Control	2.4±1.25	4.6±2.50	0.0001[a,γ]
		p***	0.939[δ]	0.0001[a,δ]	-
	Total	Experimental	9.2±3.70	4.2±2.55	0.0001[a,γ]
		Control	8.2±4.99	10.1±4.88	0.02[b,γ]
		p***	0.212[δ]	0.0001[a,δ]	-
Symptom distress	Nausea	Experimental	2.4±1.10	1.2±0.71	0.0001[a,γ]
		Control	2.2±1.28	2.7±1.06	0.034[b,γ]
		p***	0.568[δ]	0.0001[a,δ]	-
	Vomiting	Experimental	2.3±1.13	1.3±0.99	0.0001[a,γ]
		Control	1.6±1.25	2.3±1.32	0.009[b,γ]
		p***	0.012[*,δ]	0.0001[a,δ]	-
	Retching	Experimental	2.1±1.15	1.1±0.57	0.0001[a,γ]
		Control	2.2±1.22	2.5±1.38	0.091[γ]
		p***	0.863[δ]	0.0001[a,δ]	-
	Total	Experimental	6.9±2.99	3.6±1.71	0.0001[a,γ]
		Control	6.1±3.09	7.5±3.12	0.005[b,γ]
		p***	0.397[δ]	0.0001[a,δ]	-

*RINVR: Rhodes Index of Nausea, Vomiting and Retching, **intergroup, ***correlation test between group, [a]p<0.001, [b]p<0.05, [δ]: Mann-Whitney U test; [γ]: Wilcoxon Signed-Rank test, SD: standard deviation.

Study Limitations

This study was a single-site experimental study. The sample size was relatively small. Therefore, our results cannot be generalized to the population. The questionnaire was conducted only with those patients who were receiving their second chemotherapy treatment. This study only followed up these chemotherapy patients for up to four weeks; thus, the sustained effect of the application in this study needs to be tested further.

CONCLUSION

In this study, the positive effects of reflexology practice applied by nurses on nausea, vomiting, retching and sleep quality in lung cancer patients were emphasized. In line with the results we have obtained, we can make the following recommendations:

MAIN POINTS

- to increase the awareness of nurses about foot reflexology in the management of nausea, vomiting and sleep problems of patients receiving cancer chemotherapy,

Table 3. The Pittsburgh Sleep Quality Index mean score distributions according to foot reflexology practices of the patients in the experimental and control groups (n=60)

PSQI*		Before reflexology	After reflexology	p**
		Mean ± SD	Mean ± SD	
Subjective sleep quality	Experimental	1.7±0.68	1.3±0.53	0.0001[a,γ]
	Control	1.9±0.91	2.1±0.84	0.218[γ]
	p***	0.322[δ]	0.0001[a,δ]	-
Sleep latency	Experimental	2.5±0.78	1.8±0.79	0.0001[a,γ]
	Control	2.1±1.05	2.3±1.02	0.206[γ]
	p***	0.156[δ]	0.019[b,δ]	-
Sleep duration	Experimental	0.9±1.09	0.6±0.97	0.024[b,γ]
	Control	1.2±1.33	1.1±1.29	0.732[γ]
	p***	0.401[δ]	0.093[δ]	-
Habitual sleep efficiency	Experimental	2.0±1.08	1.5±1.14	0.01[b,γ]
	Control	1.4±1.43	1.8±1.35	0.026[c,γ]
	p***	0.057[δ]	0.542[δ]	-
Sleep disturbances	Experimental	1.8±0.65	1.3±0.53	0.0001[a,γ]
	Control	1.6±0.061	1.6±0.61	0.739[γ]
	p***	0.227[δ]	0.012[b,δ]	-
Use of sleeping medications	Experimental	1.0±1.14	0.6±0.76	0.013[c,γ]
	Control	0.93±1.23	0.8±1.1	0.535[γ]
	p***	0.48[δ]	0.922[δ]	-
Daytime dysfunction	Experimental	1.67±1.18	0.73±1.01	0.002[b,γ]
	Control	1.7±1.18	1.63±1.1	0.743[γ]
	p***	0.896[δ]	0.002[b,δ]	-
PSQI total	Experimental	11.83±4.16	8±3.33	0.000[a,γ]
	Control	11±5.3	11.47±4.43	0.467[γ]
	p***	0.480[δ]	0.002[b,δ]	-

[δ]: Mann-Whitney U test; [γ]: Wilcoxon Signed-Rank test, SD: standard deviation.

- to extend foot reflexology practices in the management of nausea, vomiting, retching and sleep problems of patients receiving cancer chemotherapy and to reflect this in patient care,
- to include foot reflexology treatment for patients receiving cancer chemotherapy and evidence-based studies on this subject in the nursing education curriculum.

ETHICS

Ethics Committee Approval: Permission was obtained from the Karadeniz Teknik University Faculty of Medicine Clinical Research Ethics Committee (approval number: 24237859\291, date: 31.05.2016) in order to carry out this research. This study conformed to the principles of the declaration of Helsinki.

Informed Consent: Informed consent forms outlining the aims and procedures of this study were obtained from all participants who were guaranteed confidentiality.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.P., S.H., Design: H.P., S.H., Supervision: H.P., S.H., Fundings: H.P., S.H., Materials: H.P., S.H., Data Collection and/or Processing: H.P., S.H., Analysis and/or Interpretation: H.P., S.H., Literature Search: H.P., S.H., Writing: H.P., S.H., Critical Review: H.P., S.H.

DISCLOSURES

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

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RESEARCH ARTICLE

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Molecular Identification of *Campylobacter* Species Isolated from Patients with Gastroenteritis in Edirne, Turkey

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Abstract

BACKGROUND/AIMS: *Campylobacter* is a major cause of foodborne diarrheal disease, and the incidence of campylobacteriosis has significantly increased in both developed and developing countries. The purpose of the present study was to identify the species of *Campylobacter* isolates and to evaluate the distribution of *Campylobacter* infections according to various characteristics in our region.

MATERIALS AND METHODS: *Campylobacter* isolates obtained from patients at a tertiary hospital in Edirne, Turkey were included in this study. The distribution of *Campylobacter* infections was evaluated according to age, season, and gender. Species identification was performed by multiplex polymerase chain reaction (PCR). The RNA polymerase beta-subunit gene (*rpoB*) of selected samples was amplified, and DNA sequencing was performed.

RESULTS: *Campylobacter* species were isolated from 226 (4.3%) of the 5,241 samples. One hundred and seventy-six (89.3%) of 197 samples were identified as *C. jejuni* and 19 (9.6%) as *C. coli* by multiplex PCR. Two isolates showed a band profile compatible with both *C. jejuni* and *C. coli*. DNA sequencing was performed for 21 isolates. Sixteen isolates were compatible with *C. jejuni* and 5 isolates were consistent with *C. coli*. There was no statistically significant difference in *Campylobacter* isolation rates according to gender and season ($p>0.05$). *Campylobacter* species were most frequently isolated from children in the age group of 0-14 years ($p<0.01$).

CONCLUSION: *Campylobacter* is one of the main causes of diarrhea in Turkey, and this infection is more common in children. This study contributes to information about the situation of *Campylobacter* infection and the genetic features of isolates in Turkey.

Keywords: *Campylobacter*, multiplex PCR, DNA sequencing, Turkey

INTRODUCTION

Campylobacter species are Gram-negative bacteria that are a major cause of gastroenteritis around the world.[1] Although the primary reservoirs of *Campylobacter* species are poultry, cattle, and pigs, these bacteria can be colonized in the gastrointestinal tract of many warm-blooded animals.[2] Transmission to humans is often caused by ingestion of contaminated food or water or by contact with fecal material from infected animals or people.[3] To date, 32 *Campylobacter* species and 9 subspecies have been isolated from various sources. However, the majority of human infections are caused by *C. jejuni* and *C. coli*.[4] In recent years, infections caused by *Campylobacter* species have increased in both developed and developing countries.[1] The infection occurs especially in children younger than 5. However, high incidence can also be seen in other age

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groups.[3,5] According to "The European Union One Health 2019 Zoonoses Report", there was a seasonality in campylobacteriosis cases, with peaks in the summer months.[6]

The aim of this study was to determine the distribution of *Campylobacter* species and to evaluate the effect of age, gender and seasonality on *Campylobacter* infections.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the Ethical Committee of Trakya University Faculty of Medicine (approval number: TUTF-BAEK 2016/196).

Bacterial Isolates

Campylobacter isolates obtained from 5,241 fecal samples by conventional methods at the Trakya University Health Center for Medical Research and Practice, Microbiology Laboratory between October, 2013 and May, 2016 were included in this study. Fecal samples were streaked on *Campylobacter* agar (Becton Dickinson, USA) containing 7% horse blood and incubated at 42 °C in a microaerophilic atmosphere for 48 hours. Gram staining, and catalase and oxidase tests were performed on suspected colonies to identify the *Campylobacter* species. Gram-negative, curved rods with positive catalase and oxidase tests were considered to be *Campylobacter*. Laboratory records were examined retrospectively, and the data were evaluated in terms of age, gender, and seasonal distribution.

DNA Extraction

DNA isolation of *Campylobacter* strains that were subcultured and stored at -20 °C was performed using the Invitrogen PureLink Genomic DNA Mini Kit (ThermoFisher Scientific, Waltham, MA, USA) according to the manufacturer's protocol.

Identification of *Campylobacter* Species

A multiplex polymerase chain reaction (PCR) was performed according to the protocol established by Wang et al.[7] with minor modifications. Each multiplex PCR tube contained 2.5 µL of 10X Taq buffer [100 mM Tris-HCl (pH 8.8), 500 mM KCl, 0.8% (v/v) Nonidet P40], 0.2 mM dNTP, 2 mM $MgCl_2$, 0.5 µM *C. jejuni* and *C. lari* primers, 1 µM *C. coli* primers, 2 µM *C. upsaliensis* primers, 0.2 µM 23S rRNA primers, 1.25 U of Taq DNA polymerase (ThermoFisher Scientific, Waltham, MA, USA), and 2.5 µL of whole-cell template DNA in total 25 µL reaction volume. The primers used for the identification of *Campylobacter* species are shown in Table 1. In all PCR reactions, *C. jejuni* NCTC 13367 and *C. coli* NCTC 11350 were used as positive controls, and *E. coli* ATCC 25922 was used as a negative control. PCR products were subjected to electrophoresis on 1.5% agarose gel, and the bands were evaluated under ultraviolet light.

DNA Sequencing

DNA sequencing was performed for 21 isolates. According to the multiplex PCR results, 13 *C. jejuni* and 6 *C. coli* isolates were randomly selected for DNA sequencing. Sequence analysis was also performed on two samples exhibiting double bands. The RNA polymerase beta-subunit gene (*rpoB*) was amplified using the previously described primers.[8] PCR products were purified using the Invitrogen PureLink Quick PCR Purification Kit (ThermoFisher Scientific, Waltham, MA, USA). DNA sequencing was performed by the Trakya University Technology Research Development Application and Research Center. The *rpoB* gene sequence analysis was carried out on the Applied Biosystems 3500 Series Genetic Analyzer (ThermoFisher Scientific, Waltham, MA, USA) using the Applied Biosystems BigDye Terminator v3.1 Cycle Sequencing Kit (ThermoFisher Scientific, Waltham, MA, USA). The sequencing chromatograms were analyzed using the ProSeq v2 and BioEdit programs. The nucleotide sequences of the isolates were compared with sequences in GenBank using the Basic Local Alignment Search Tool.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 software (Kaysville, Utah, USA) was used for statistical analysis. Data were analyzed by descriptive statistical methods. Qualitative data were compared by Pearson chi-square and the Fisher-freeman-halton exact test with a significance level of $p<0.05$.

RESULTS

Bacterial Isolates

A total of 5,241 stool samples were sent to the microbiology laboratory for *Campylobacter* culture between October, 2013 and May, 2016. *Campylobacter* spp. were detected in 226 (4.3%) of these samples, which were obtained from 215 individual patients. Of the patients with *Campylobacter* infection, 44.2% were female and 55.8% were male. There was no statistically significant difference in *Campylobacter* isolation rate by gender ($p=0.584$), and the difference in seasonal rates of *Campylobacter* isolation was not statistically significant ($p=0.141$) (Table 2). The highest culture positivity rate was detected in May ($p=0.001$), while the lowest rate was seen in September ($p=0.014$) (Figure 1). When the 0-5 and 6-14 age groups were evaluated together, *Campylobacter* spp. were isolated more frequently in the 0-14 age group compared to the other age groups ($p<0.01$) (Figure 2).

Identification of *Campylobacter* Species

Bacterial DNA was obtained from 197 isolates of 187 patients. By multiplex PCR, 176 (89.3%) isolates were identified as *C. jejuni* and 19 (9.6%) isolates as *C. coli*. Two samples showed a band profile compatible with both *C. jejuni* and *C. coli*.

DNA Sequencing

The results of the DNA sequencing of 21 isolates were evaluated. The DNA sequences of 13 isolates were found to be compatible with the *C. jejuni* sequences in the GenBank. The DNA sequences of the five isolates

Table 1. Primers used for the identification of *Campylobacter* species (Wang et al.[7])

Oligonucleotide primers	Amplicon size (bp)
23SF: 5'- TATACCGGTAAGGAGTGCTGGAG-3' 23SR: 5'- ATCAATTAACCTTCGAGCACCG-3'	650
CJF: 5'-ACTTCTTTATTGCTTGCTGC-3' CJR: 5'-GCCACAACAAGTAAAGAAGC-3'	323
CCF: 5'-GTAAAACCAAAGCTTATCGTG-3' CCR: 5'-TCCAGCAATGTGTGCAATG-3'	126
CLF: 5'-TAGAGAGATAGCAAAAGAGA-3' CLR: 5'-TACACATAATAATCCCACCC-3'	251
CUF: 5'-AATTGAAACTCTTGCTATCC-3' CUR: 5'-TCATACATTTTACCCGAGCT-3'	204

matched *C. coli*. One isolate was identified as *C. coli* by multiplex PCR and *C. jejuni* by sequence analysis. Additionally, both of the isolates showing double bands in multiplex PCR were found to be compatible with *C. jejuni*. One of the *C. coli* isolates was submitted to the DNA Data Bank of Japan database (accession no: LC511784). The results of multiplex PCR and sequencing analysis of the isolates included in DNA sequencing are shown the Table 3.

DISCUSSION

Campylobacter is one of the most common causes of diarrheal diseases worldwide.[9] There has been a significant increase in the incidence of campylobacteriosis in North America, Europe, and Australia. Although epidemiological data are insufficient, it is known that campylobacteriosis is endemic in Africa, Asia, and the Middle East.[1] In European Union countries, 220,682 cases (59.7 per 100,000 population) were reported in 2019.[6] In a study performed in Denmark, it was found that the incidence of *Campylobacter* infection was higher in males. For domestic cases, age groups 20-29 and 0-4 years had a higher incidence compared to other age groups. For travel-related cases, the incidence was highest in young adults aged 20-29 years. Also, it was revealed that cases not related to travel increased from May to October and peaked in August.[5] In a study conducted in the United States, the highest incidence of campylobacteriosis was observed in males and children under five years of age in most regions, while in three states, the highest incidence was found in people over 60 years of age. The incidence was highest from June to August and lowest from December to February for all regions and age groups.[10] In Ireland, the highest incidence of *Campylobacter* infection was reported in children aged 0-4 years. Cases reported in males were more than female cases in the surveillance system.[11] In our study, 44.2% of the patients with *Campylobacter* infection were female, and 55.8% of the patients were male; but no statistically significant difference was found by gender (p>0.05). Infection most commonly occurred in May (p=0.001), and least commonly in September (p=0.014); nonetheless, we observed no seasonal patterns. The majority of cases were detected in children, and these data are consistent with other studies in Turkey.[12-14]

C. jejuni is responsible for the majority (85-95%) of human *Campylobacter* infections, and *C. coli* is the second most common (5-10%) species.[3,15] Kayman et al.[13] isolated thermophilic *Campylobacter* spp. from 5.4% of 3,287 stool samples of patients with gastroenteritis; and using multiplex PCR, they identified 85% of the isolates as *C. jejuni* and 15% as *C. coli*. In a study performed in Iran, 420 fecal samples from hospitalized children were analyzed. In 8.8% of these samples, the authors isolated *Campylobacter* spp. In that study, 75.7% of *Campylobacter* isolates were

Table 2. Distribution of *Campylobacter* isolates according to gender and season, Edirne, 2013-2016

Parameters	No. sampled (%)	No. positive (%)	p-value
Gender			
Female	2,412 (46.0)	100 (44.2)	0.584
Male	2,829 (54.0)	126 (55.8)	
Season			
Winter	1,362 (26.0)	56 (24.8)	0.141
Spring	1,635 (31.2)	86 (38.0)	
Summer	1,003 (19.1)	38 (16.8)	
Autumn	1,241 (23.7)	46 (20.4)	
Total	5,241 (100)	226 (100)	

*statistical significance defined as p≤0.05.

Table 3. Results of multiplex PCR and sequencing analysis of the isolates included in DNA sequencing

Sample no.	Multiplex PCR	DNA sequencing	
		Matched sequence (accession no.)	Identity (%)
1-10	*C. jejuni*	*C. jejuni* (CP028910)	100
11	*C. jejuni*	*C. jejuni* (DQ174200)	100
12	*C. jejuni*	*C. jejuni* (HM486854)	100
13	*C. jejuni*	*C. jejuni* (AF372097)	100
14-17	*C. coli*	*C. coli* (AF372098)	100
18	*C. coli*	*C. coli* (HG326877)	98
19	*C. coli*	*C. jejuni* (CP054847)	99
20	*C. jejuni* and *C. coli* (double bands)	*C. jejuni* (CP012217)	100
21	*C. jejuni* and *C. coli* (double bands)	*C. jejuni* (CP053854)	100

PCR: polymerase chain reaction.

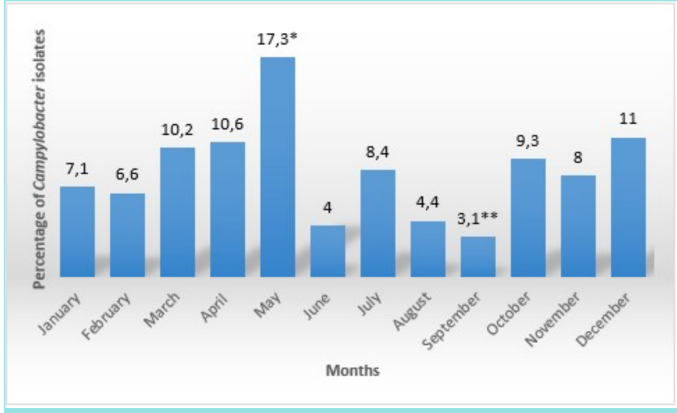

Figure 1. Distribution of *Campylobacter* isolates by month, Edirne, 2013-2016.
*p=0.001, **p=0.014.

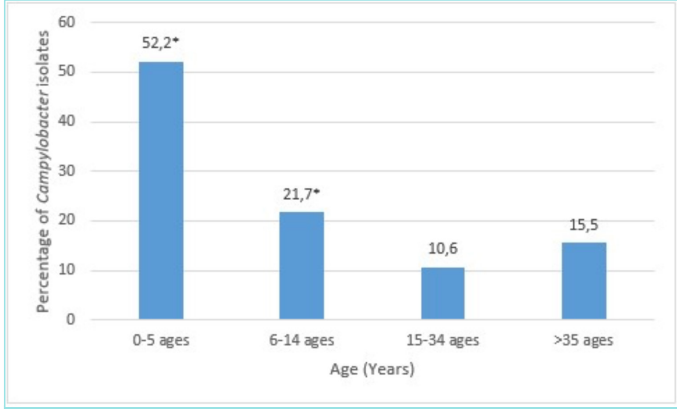

Figure 2. Distribution of *Campylobacter* isolates by age group, Edirne, 2013-2016.
*p<0.01.

identified as *C. jejuni* and the remaining isolates were identified as *C. coli*.[16] In a study carried out in Edirne in 2005, *Campylobacter* was detected in 4% of fecal samples sent to the microbiology laboratory in our hospital, and 81% of these strains were *C. jejuni*. *Campylobacter* was detected mostly in July, August, and September, and there were no differences between age groups and gender distributions.[17] In our study, *Campylobacter* spp. was detected in 4.3% of the samples sent to the laboratory for stool culture. Multiplex PCR identified 89.3% and 9.6% of the isolates to be *C. jejuni* and *C. coli*, respectively. Two isolates showed a band profile compatible with both *C. jejuni* and *C. coli* reference strains. In terms of *Campylobacter* isolation rate and species distribution, our results are consistent with those of other studies conducted in Turkey and elsewhere.[13,15] However, we considered that the inclusion of *Campylobacter* isolates obtained from patients admitted to the single-center to be a limitation of this study. The *rpoB* gene is used in the species identification and phylogenetic analysis of *Campylobacter*. However, *rpoB* gene sequencing may lead to misidentification between the two closely related species, *C. jejuni* and *C. coli*.[8,18] In our study, one isolate showed a band profile consistent with *C. coli* in multiplex PCR, and this isolate was identified as *C. jejuni* by sequence analysis.

CONCLUSION

Campylobacter is a significant bacterial agent in gastroenteritis; therefore, it is important to investigate *Campylobacter* in routine laboratory diagnosis. In the present study, it was determined that there was no statistically significant difference in *Campylobacter* isolation rates according to gender and season in our region. However, it was observed that *Campylobacter* infection is more common in children. This study contributes to information about the epidemiological features of *Campylobacter* in Turkey. To obtain more comprehensive epidemiological data about *Campylobacter* infection and examine the the genetic features of *Campylobacter*, there is a need for further research conducted over an extended period and which uses multiple molecular methods.

MAIN POINTS

- *Campylobacter* species were isolated from 4.3% of the fecal samples.
- The most common *Campylobacter* species isolated from fecal samples was *C. jejuni* (89.3%) followed by *C. coli* (9.6%).
- No statistically significant difference was found in the *Campylobacter* isolation rate according to gender and season ($p>0.05$).
- *Campylobacter* species were most commonly isolated from children aged 0-14 years ($p<0.01$).

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ETHICS

Ethics Committee Approval: This study was approved by the Ethical Committee of Trakya University Faculty of Medicine (approval number: TUTF-BAEK 2016/196).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.E., N.Ş., K.T., M.C.U., Ş.B., Design: C.E., N.Ş., K.T., M.C.U., Ş.B., Supervision: C.E., N.Ş., K.T., Materials: C.E., N.Ş., Ş.B., Data Collection and/or Processing: C.E., N.Ş., M.C.U., Analysis and/or Interpretation: C.E., N.Ş., K.T., M.C.U., Literature Search: C.E., Ş.B., Writing: C.E., Critical Review: N.Ş., K.T.

DISCLOSURES

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

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RESEARCH ARTICLE

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Prognostic Nutritional Index as a Predictor of In-Hospital Mortality in Patients with Ischemic Hepatitis

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Abstract

BACKGROUND/AIMS: Ischemic hepatitis (IH), a life-threatening medical disease, requires treatment in the shortest possible time. The present study aimed to investigate the clinical significance of the prognostic nutritional index (PNI) for IH.

MATERIALS AND METHODS: We retrospectively analyzed 40 patients admitted to our hospital with a diagnosis of IH. The patients were classified into two groups (survivals and non-survivals) and they were compared according to their clinical and laboratory characteristics. PNI was calculated as 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm^3). We also used a logistic regression to identify any risk factors of in-hospital mortality.

RESULTS: The mean age of the study cohort was 72±12 years. Of the patients, 25 (64.1%) were male, and 21 (52.5%) died during their intensive coronary unit stay. The PNI levels were significantly lower in the non-survival group than in the survival group (40.9±6.7 vs 32.9±5.8, $p<0.001$). Multivariate analysis showed that the PNI [odds ratio (OR): 0.98, 95% confidence interval (CI): 0.97-0.99, $p\leq0.001$], glucose (OR: 2.54, 95% CI: 1.64-4.29, $p\leq0.001$), albumin (OR: 0.93, 95% CI: 0.91-0.996, $p\leq0.001$), red cell distribution width (OR: 0.99, 95% CI: 0.98-0.99, $p\leq0.001$) independently predicted in-hospital mortality.

CONCLUSION: The PNI is an independent predictor of in-hospital mortality in patients with a diagnosis of IH.

Keywords: Hepatitis, in-hospital mortality, nutritional index

INTRODUCTION

Ischemic hepatitis (IH) is a life-threatening syndrome characterized by a rapid, massive and transient rise in the plasma aminotransferase level [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] as a result of predisposing conditions, such as cardiac failure, sepsis and respiratory failure. In its diagnosis, other causes of higher transaminase levels need to be excluded, including acute viral hepatitis, metabolic liver diseases and toxic hepatitis.[1-3] IH is a frequent cause of acute liver injury in intensive care units, with previously reported incidences of nearly 2.5%, but it has also been reported in some studies that its incidence can be as high as 10% and it results in a mortality rate of 56% to 59% depending on the awareness of the clinical picture.[4]

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Evidence suggests that the cross-impact between the liver and other organ systems is a major factor in the development of IH, but the pathophysiologic mechanisms are not fully understood yet.

The prognostic nutritional index (PNI) is a derivative of the total lymphocyte count and serum albumin, reflecting the nutritional and inflammatory status of the patients.[5] PNI is a prognostic score and it has a very close relationship with prognosis in a variety of clinical settings including cardiovascular diseases, infectious diseases and cancer.[6-11] In this study, we aimed to investigate the prognostic value of PNI in patients with IH.

MATERIALS AND METHODS

Study Population

Between January, 2017 and November, 2019, 52 patients with the diagnosis of IH were hospitalized in the intensive care, gastroenterology, or cardiology departments of our hospital. The medical records of these patients were retrospectively evaluated. Twelve patients were excluded from this study; one patient was under the age of 18; two patients were diagnosed with cancer and nine patients had missing information in their hospital data.

The diagnostic criteria for IH were determined as follows: rapid, massive and transient increases in either AST or ALT up to 10 times the upper limit of normal, and the presence of predisposing factors such as cardiac, circulatory and/or respiratory failures. Additionally, some tests were examined in terms of the diagnosis and differential diagnosis of IH. Echocardiographic findings including measurements of ventricular and valve functions, heart size and pulmonary artery pressure were examined for cardiac causes. Liver size and condition, vascular structures and flow conditions, and the spleen were evaluated by abdominal ultrasonography. When necessary, liver and vascular structures were evaluated, pancreatitis was ruled out, and cirrhosis symptoms were examined by computed tomography.

Other causes in the differential diagnosis of acute liver enzyme elevation, and tests related to toxic, viral and autoimmune hepatitis were examined.

- Information obtained from the patients and their relatives about toxins, drugs and/or herbal medicines which cause acute serum aminotransferase elevation were considered. When necessary, toxicological examinations which could be compatible with the clinic were performed.

- Since autoimmune hepatitis can also present with acute hepatitis clinic, tests such as anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney-microsomal, anti-soluble liver antigen, globulin profile, anti-neutrophil cytoplasmic antibody, HLA typing were performed.

- Hepatitis A, hepatitis B, hepatitis C, cytomegalovirus and Ebstein-Barr virus tests were requested in relation to viral hepatitis.

This study was approved by the Ethics Committee for Clinical Research of the Ordu University Faculty of Medicine (approval number: 2020/207).

Laboratory Analysis

In the retrospective analysis of the patients' records, the diagnosis of IH was made considering the highest ALT-AST levels detected during their hospitalization. Other biochemical and hematological parameters, viral markers, infectious diseases, hepatobiliary ultrasound and transthoracic echocardiography were also examined to evaluate the reasons which may have caused liver enzyme elevation. For each case, the PNI was calculated with the following equation; PNI = [10 x albumin (mg/dL)] + [0.005 x lymphocyte count (per mm^3)].

Statistical Analysis

All statistical analyses were performed with the SPSS 21 software package (SPSS Inc., Chicago, Illinois). Quantitative variables with a normal distribution are given as mean (± standard deviation), while those without a normal distribution are presented as median and minimum-maximum values. Categorical variables are shown as percentage. The normality of the data was determined using the Kolmogorov-Smirnov test. The t-test was used to compare quantitative variables with the normal distribution, while the Mann-Whitney U test was employed to compare data without normal distribution. The chi-square test was performed to compare categorical variables. Independent predictors of in-hospital mortality were identified using logistic regression analysis. All variables showing significance values of less than 0.10 in the univariate analysis were included in the model. Two-tailed p-values of less than 0.05 were considered as statistically significant.

RESULTS

The study population included 40 patients with IH. The mean age of the study cohort was 72±12 years. Of the patients, 25 (64.1%) were male, and 21 (52.5%) died during their stay in the intensive care unit. Heart failure was the main factor for the development of IH in 24 patients (62%). Sepsis caused IH in eight patients (20%). Four patients (10%) developed IH due to hemorrhage and hypovolemia. There was no significant difference between the 2 groups in terms of hypoperfusion etiologies. The PNI levels were significantly lower in the non-survival group compared to the survival group (40.9±6.7 vs 32.9±5.8, $p<0.001$). The clinical characteristics of all patients enrolled in the study are shown in Table 1. The multivariate analysis showed that the PNI [odds ratio (OR): 0.98, 95% confidence interval (CI): 0.97-0.99, $p\leq0.001$], glucose (OR: 2.54, 95% CI: 1.64-4.29, $p\leq0.001$), albumin (OR: 0.93, 95% CI: 0.91-0.996, $p\leq0.001$), and red cell distribution width (OR: 0.99, 95% CI: 0.98-0.99, $p\leq0.001$) independently predicted in-hospital mortality (Table 2).

DISCUSSION

In our study, we determined that the PNI value was significantly lower in the non-survival group than in the survival group, and that PNI was a predictor for mortality due to IH.

IH is a serious and uncommon form of hypoxic hepatitis accompanied by elevated liver enzymes, and increased lactate dehydrogenase (LDH) levels due to life threatening predisposing factors including heart failure, respiratory diseases and sepsis. Physicians need to consider this diagnosis in unexplained extreme elevations of liver transaminases where there are elevations up to 10 times the upper limit of normal, especially in the presence of risk factors. As a general rule, transaminitis occurs 1 to 3 days after the acute disturbing event and generally normalizes 7 to 10 days later. In addition, the ALT to LDH ratio is almost always less than 1.5.[6]

Previous studies have shown that impaired liver function tests are common in patients with acute heart failure and they are associated

Table 1. Baseline characteristics of the study population at admission

Variables	Survivors (n=19)	Non-survivors (n=21)	p-value
Age (years)	70.4 ±13.1	74.6±11.1	0.27
Glucose (mg/dL)	128.15 (55.67)	187.09 (88.23)	0.17
AST (U/L)	1,155.47 (1652.26)	1,268.90 (1014.62)	0.22
ALT (U/L)	800.78 (786.33)	734.71 (524.99)	0.75
Alkaline phosphatase (U/L)	128.15 (72.04)	157.14 (140.5)	0.64
Total protein (g/dL)	6.22 (0.69)	5.76 (1.22)	0.23
Albumin (g/dL)	3.67 (0.63)	2.82 (0.69)	0.001
Total bilirubin (mg/dL)	2.48 (1.91)	2.18 (1.83)	0.94
Direct bilirubin (mg/dL)	1.43 (1.17)	1.60 (1.59)	0.71
GGT (U/L)	129.23 (154.11)	165.71 (375.71)	0.12
LDH (U/L)	1,011.05 (921.65)	1,102.31 (815.12)	0.75
C-reactive protein (mg/dL)	32.31 (45.4)	24.01 (32.87)	0.50
Urea (mg/dL)	90.15 (44.87)	144.71 (78.32)	0.11
Creatinine (mg/dL)	2.17 (1.52)	3.2 (2.77)	0.27
Hemoglobin, (g/dL)	11.99 (2.23)	10.44 (2.41)	0.43
Hematocrit, (%)	36.6±6.3	32.6±7.4	0.76
White blood cell count ($X10^3$/µL)	9.75 (3.08)	15.03 (10.96)	0.26
Lymphocyte ($X10^3$/µL)	1.05 (0.45)	1.01 (0.82)	0.35
Neutrophyl ($X10^3$/µL)	7.99 (3.11)	13.3 (10.4)	0.38
Platelet ($X10^3$/µL)	191.73 (102.87)	154.33 (73.77)	0.19
RDW, (%)	31.6 (17.08)	25.71 (15.33)	0.51
TSH (mU/L)	1.26 (1.84)	0.64 (1.48)	0.25
Troponin T (µg/L)	0.16 (0.27)	0.91 (2.18)	0.13
Creatinine kinase (U/L)	259.27 (447.51)	661.61 (1363.38)	0.45
PH	7.3±0.7	7.2±0.1	0.48
Lactate (mmol/L)	3.16 (1.62)	5.64 (3.81)	0.36
Bicarbonate (mEq/L)	21.2±3.4	19.3±5.82	0.33
PNI	40.9±6.7	32.9±5.8	0.01
Ejection fraction, (%)	40.5±15.7	38.6±13.9	0.76
sPAP (mmHg)	41.8±12.5	51.4±11.3	0.17
Length of stay (days)	8.83 (6.41)	21.57 (25.68)	0.48
Etiology			
Heart failure (n, %)	10 (52.6)	14 (66.6)	0.38
Sepsis (n, %)	3 (15.7)	5 (23.3)	
Hypovolemia (n, %)	3 (15.7)	1 (4.7)	
Other (n, %)	3 (15.7)	1 (4.7)	

The differences were regarded as significant when p<0.05.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, PNI: prognostic nutritional index, RDW: red cell distribution width, sPAP: systolic pulmonary artery pressure, TSH: thyroid-stimulating hormone.

Table 2. Independent predictors of in-hospital mortality in patients with ischemic hepatitis: logistic regression analysis

Variables	Univariate OR, 95% CI	p-value	Multivariate OR, 95% CI	p-value
Glucose	3.12 (1.92-4.54)	<0.001	2.54 (1.64-4.29)	<0.001
PNI	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Albumin	0.92 (0.90-0.94)	<0.001	0.93 (0.91-0.96)	<0.001
RDW	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001

The results were regarded as significant when p<0.05.
RDW: red cell distribution width, PNI: prognostic nutritional index, OR: odds ratio, CI: confidence interval.

with an increased risk of mortality, readmission, and in-hospital HF worsening.[7] In our study, the mean ejection fraction decreased in both groups. The ejection fraction was found to be slightly lower in the non-survival group than in the survival group, but this difference was not statistically significant.

Nutritional condition reflects the patients' health status. Previous studies have reported the use of multiple tools in screening for nutritional parameters in patients, such as PNI, the geriatric nutritional risk index (GNRI) and controlling nutritional status score (CONUT). Numerous studies have reported that these parameters are associated with adverse outcomes such as heart failure,[7] various cancers,[12,13] pulmonary embolism,[14] stroke[15] and chronic kidney disease.[16]

It is difficult to assess the nutritional status of patients. The data obtained by examination may differ according to the practitioner, or the verbal information obtained from the patients and/or their relatives may be misleading. Therefore, we preferred the PNI as a more objective nutritional marker. Based on laboratory data, the most commonly used nutrition indexes are CONUT, GNRI and PNI. All three indexes contain the albumin component. Albumin is a protein with a long half-life and it indicates a chronic nutritional status. IH is an acute condition. However, we examined the effect of chronic malnutrition on acute IH by measuring the PNI of patients at the time of admission. Malnutrition is a complex condition involving the depletion of protein and energy stores, resulting in a weakened immune defense.

The present study revealed that the PNI value and serum albumin level on admission were independently associated with mortality. PNI is derived from an equation including the albumin value and the lymphocyte count. Multivariate analysis revealed that PNI and serum albumin were significant predictors of mortality in IH patients. In our study, no difference was found between the survival and non-survival groups in terms of their lymphocyte levels. The factor making the difference between the PNI values was the albumin levels.

Recent studies have shown that low serum albumin levels, which are used as an indicator of nutritional status in clinical practice, predict hospitalization and mortality. Various mechanisms may mediate low serum albumin levels in IH. Since it is synthesized in hepatocytes, low albumin levels indicate impaired liver function. Albumin levels may also be altered with inflammation. Proinflammatory cytokines, such as interleukin-6 or tumor necrosis factor-alpha, affect albumin synthesis in hepatocytes leading to malnutrition.[17,18] In addition, inflammatory responses accelerate catabolism, resulting in low albumin levels.[19] In critical illnesses, decreased appetite, inadequate intake, and malabsorption also lead to low albumin levels.[20]

Study Limitations

The limited sample size and retrospective design are the limitations of our study. As it was conducted retrospectively, we were not able to determine vital signs at admission, treatments and nutritional support during hospitalization. The inability to compare the hypoperfusion time is an important limitation of our study. Since our study was retrospective, we could not obtain data on this subject. However, in a previous study of IH, only 51% of the patients had a documented hypotensive event or shock state.[21] Namely, the hypoferfusion time would be very difficult to determine.

CONCLUSION

In conclusion, lower PNI values are independently associated with in-hospital mortality in IH patients. The PNI may be a useful parameter for predicting mortality in IH patients.

MAIN POINTS

- IH is a serious and uncommon form of hypoxic hepatitis accompanied by elevated liver enzymes, and increased LDH levels due to life threatening predisposing factors including heart failure, respiratory diseases or sepsis.
- The PNI is a prognostic score reflecting immune and inflammatory status and it has a very close relationship with the prognosis in a variety of clinical settings such as cardiovascular diseases, infectious diseases, and cancer.
- In our study, we found that the PNI value was significantly higher in the non-survival group than in the survival group, and also, it was a predictor for mortality due to IH.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee for Clinical Research of the Ordu University Faculty of Medicine (approval number: 2020/207).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Y., Design: A.V., M.Y., Supervision: Ö.T., Materials: H.M.Ö., Data Collection and/or Processing: M.A.A., Analysis and/or Interpretation: A.V., Literature Search: Z.Y.G., Writing: A.V., T.A., Critical Review: A.V.

DISCLOSURES

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

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RESEARCH ARTICLE

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Evaluation of Patient Safety Culture of Nurses in Northern Cyprus

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Abstract

BACKGROUND/AIMS: Patient safety culture is the outcome of values, perceptions, attitudes, skills and behaviors of an individual or group that determine the style, competence and promises of an institution in health and safety management. Nurses play an important role in improving quality in health care through initiatives and strategies for patient safety. This study was conducted to evaluate patient safety culture in nurses working in a university hospital in Northern Cyprus.

MATERIALS AND METHODS: This survey was planned as a cross-sectional descriptive study and 130 nurses were included in the sampling. The survey data were collected using the Personal Information Form and the Patient Safety Culture Scale (PSCS).

RESULTS: In this study, the total mean score of the nurses from the PSCS was 2.82±0.44. The mean scores of the nurses' subscales related to PSCS were determined as follows: 2.88±0.54 in the "care environment", 2.83±0.56 in the "employee behavior", 2.83±0.59 in the "employee training", 2.81±0.50 in the "management and leadership", and 2.68±0.54 in the "unexpected incident and error reporting" subscales. The total Cronbach's alpha reliability coefficient of the scale was 0.963 and between 0.807-0.963 for the subscales.

CONCLUSION: It was determined that the nurses' PSCS scores were above the average level. Developing a patient safety culture in institutions is important for quality improvements which are rapidly advancing in healthcare services nowadays.

Keywords: Patient safety, patient safety culture, nurse

INTRODUCTION

Worldwide, patient safety, which is a fundamental principle of health care, is receiving increased attention.[1,2] The safety of health care is a major global concern today.[2] "*To err is human*" was a report published in 1999 by the institute of medicine, in which it is estimated that approximately 98,000 people died each year in the United States of America (USA) because of medical errors.[3,4] Medical errors account for 9.5% of all deaths in the USA. Medical errors were reported to be the third most common cause of death after heart disease and cancer.[4,5] When the root causes of medical errors were examined, the errors were caused by problems related to the system, such as organizational structure, technical infrastructure and inadequate human power.[6,7] In this regard, the World Health Organization formed a patient safety unit in 2004 and the practices for patient safety were begun to be carried out more systematically.[8-10]

The prevention of health-related errors and the elimination of problems caused by these errors depend on the formation of patient safety culture.[11] Patient safety culture is the product of the values, perceptions, attitudes, skills and behaviors of the individuals or groups

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which determine the style, competence and promises of an institution in health and safety management.[12,13] Safety culture is based on three main principles including trust, reporting and improvement.[7] A positive safety culture involves effective teamwork, communication, a non-punitive approach towards errors, and cooperative learning.[14] In this regard, it is important to believe that mutual trust-based communication, common perceptions of safety and preventive measures are beneficial. In order to develop the safety culture of an institution, it is necessary that all of the employees of the institution have knowledge about these safety implementations, take an active role in their implementations and work as a team.[15]

Nurses, one of the important elements of patient safety culture, are an important professional group actively working in all areas of the health system.[16] In the delivery of health services, nurses constitute the largest proportional group of all healthcare personnel and at the same time provide the closest and most continuous care services to the patients. In this regard, activities that improve patient safety are significantly related to nursing care.[17] Nurses are responsible for protecting their patients from all possible hazards, and for preventing or minimizing undesirable consequences of processes and treatments applied in all environments where they serve patient care.[18]

It is necessary to evaluate the perceptions and attitudes of the nurses and all the personnel regarding patient safety in order to be able to establish and improve patient safety culture, and this evaluation should be repeated at regular intervals.[19] The assessment of safety culture in institutions allows for the identification of areas related to patient safety, in order to raise awareness about patient safety in personnel, to monitor changes over time in patient safety interventions, and to compare outcomes.[20]

In the literature review, no study was found on the evaluation of patient safety culture of nurses in Northern Cyprus. The definition of patient safety culture of nurses is thought to be a guide for studies on the development of patient safety culture.

Objectives of the study: This study was conducted in order to evaluate patient safety culture in nurses working in a university hospital. In this survey, answers to the following questions were investigated:

1. What is the level of the nurses' total and subscale scores in the patient safety culture questionnaire?

2. Is there any difference between the nurses' descriptive characteristics and their mean scores of the culture of patient safety scale?

MATERIALS AND METHODS

Study type: This survey was planned as a cross-sectional and descriptive study.

Setting: This study was conducted in a university hospital. Patient care in the university hospital where the survey was carried out is realized according the principles proposed by the Joint Commission International to ensure patient safety.

Population and research sample: Nurses working in the university hospital (ward, intensive care, operating room, outpatient clinic) composed the population and 130 nurses who agreed to participate in this survey were included in the research sample. The total number of nurses was 220 and the participation rate was 59.09%.

Data collection tools: Data were collected using the "Personal Information Form" and the "Patient Safety Culture Scale (PSCS)". The Personal Information Form was created to determine the socio-demographic characteristics of the nurses and it consists of 11 questions. The PSCS was developed by Türkmen et al.[6] for the evaluation of patient safety culture. In the nursing group, this scale, which had validity/reliability studies, consists of 51 items. The PSCS; consists of 5 subscales consisting of management and leadership (17 items), employee behavior (14 items), unexpected events and error reporting (5 items), employee training (7 items) and the care environment (8 items). PSCS is a four-point Likert type measuring instrument. The efficacy of patient safety practices has been assessed according to scores ranging from 1 to 4 as follows "1; *I do not agree at all*", "2; *I do not agree*", "3; *I agree*", "4; *I fully agree*". In the interpretation of the scale score, a high average score shows positive patient safety culture, and a low score indicates the presence of a negative patient safety culture. The total Cronbach's alpha reliability coefficient of the PSCS was found to be 0.97 and the sub-dimensions of the PSCS were found to be between 0.83 and 0.92. In this study, the total Cronbach's alpha reliability coefficient of the scale was 0.963 and the subscales were between 0.807 and 0.963.

Ethical considerations: Approval for this scientific research by the ethics evaluation board of the university (approval number: YDU/2016/42-348, date: 22.12.2016) and permission of the university hospital were granted for the research to be implemented.

Data collection: Data were collected between January and April, 2017 from the nurses by face-to-face interviews. After the researchers explained the purpose of the study to the nurses, written informed consent was obtained from them.

Statistical Analysis

Data obtained from this study were evaluated by the SPSS 20.0 (SPSS, Inc., Chicago, IL, USA) program. Numerical and percentile distributions, arithmetic means and standard deviations of the data were examined. Numerical data without normal distribution were subjected to the Mann-Whitney U Test. Statistical significance was accepted as $p<0.05$ at a 95% confidence interval.

RESULTS

In the present study, when the personal and professional characteristics of nurses were analyzed, it was determined that 42.3% of them were under the age of 25 (28.56±7.58 years of age mean), 85.4% of them were female, 70.0% of them were undergraduate and 71.5% of them had working experience of between 0-5 years, and 53.1% of them were working in clinics (Table 1).

Regarding the patient safety training status of the nurses, it was found that 60.8% of them had been trained about patient safety. 71.5% of all nurses participating in this study stated that they found their training for patient safety to be insufficient (Table 2).

It was found that 17.7% of the nurses needed to be trained on the correct identification of the patient, 33.1% on safe drug applications, 26.9% on transfusion safety, 30.0% on safe surgical applications, 13.8% on reducing risks resulting from falls, 23.1% of them on effective communication, 41.5% of them on radiation safety, and 33.8% of them on medical device safety (Table 3).

Table 1. Personal and occupational characteristics of the nurses (n=130)

Characteristics		n	%
	25 and below	55	42.3
Age	Between 26-30	50	38.5
Mean (28.56±7.58)	31 and above	25	19.2
Gender	Female	111	85.4
	Male	19	14.6
Educational status	Diploma in nursing	13	10.0
	Associate diploma	15	11.5
	Bachelor	91	70.0
	Postgraduate	11	8.5
Working unit	Service	69	53.1
	Outpatient clinic	20	15.4
	Intensive care	32	24.6
	Operation room	9	6.9
Total working experience	0-5 years	93	71.5
	6 years and above	37	18.5
Total		130	100.0

The mean scores and standard deviations of the PSCS and its subscales were calculated. The total score of the nurses from the PSCS was 2.82±0.44. The lowest mean subscale score was in the "unexpected incident and error reporting" subscale (2.68±0.54), and the highest was in the "care environment" subscale (2.88±0.54) (Table 4).

Comparison of the mean PSCS scores and in-service education status of the nurses showed that there were statistically significant differences in the subscales of patient safety education between PSCS and the "management and leadership", "care environment" and "employee behavior" subscales and the patient safety training status of the nurses ($p<0.05$). It was found that the mean scores were higher for those who had received in-service training in PSCS and the "management and leadership", "care environment" and "employee behavior" subscales ($p<0.05$) (Table 5).

In this study, the mean scores of the nurses and their subgroups were compared with their age and gender, their educational status, their working clinics and their occupational experience, but no statistically significant difference was found between these variables and the mean scores obtained from PSCS ($p>0.05$).

DISCUSSION

Nowadays, the formation of patient safety culture is an important goal of system-based safety development efforts.[21] This study was performed with the aim of evaluating patient safety culture in nurses.

In the present study, the mean PSCS scores of the nurses' patient safety culture was 2.82±0.44. In other studies where the same scale was used, the total score averages of the nurses' PSCS were evaluated: the score average was 3.00±0.539 in Karaca and Arslan's[22] study performed in two private hospitals and the score average was 1.88 in the study of Yolcu et al.[20] performed in eight state hospitals. In addition, the total score averaged by the nurses from the PSCS was 2.64±0.43 in the study of Rızalar et al.[13] and 2.81±0.40 in the study of Ertürk et al.[23]. In studies conducted by Erdağı and Özer[24], for the nurses' perceptions of patient safety culture, it was determined that the nurses had a moderate sense of security. The results of our study were found to be similar to these studies. Unlike our findings, in a study by Yapucu Güneş et al.[25], carried out in Turkey with 554 nurses, it was determined that nurses had a negative perception of patient safety.

The lowest score average was found in the "unexpected incident and error reporting" subscale, and the highest score average was found in the "care environment" subscale. In a study conducted by Karayurt et al.[26] to identify patient safety culture with a different scale, the "hospital interventions and change" subscale score was the highest and the "error reporting frequency" subscale score was the lowest. The results of this study are similar to our findings. The lowest score for "error reporting" does not determine that the error rate is really low.

The "care environment" subscale of the patient safety culture includes the physical structure and equipment of the institution, materials, devices and technologies, electronic medical records, barcode systems for materials and drugs, identification safety systems, and security measures at the entrances and exits of institutions. In our study, the "care environment" is the subscale (2.88±0.54) in which the nurses had the highest total PSCS total score, suggesting that the institutional care environment in which the research was conducted was effective in ensuring patient safety. The mean score of this subscale was determined to be 2.07 in the study of Yolcu et al.[20], and 2.58±0.51 in the study of Rızalar et al.[13], and the average score obtained in our study was higher than those scores. The higher score obtained from the "care environment" subscale is considered to indicate that the physical structure and equipment, material, device, technology usage and care facilities of the hospital where the study was conducted were good.

The "employee behavior" subscale includes subjects such as compliance with working rules, knowing quality criteria and institutional targets, conforming with team work, cooperation with colleagues for patient benefit, giving suggestions to improve patient safety, and informing patients and relatives when an error occurs [6] There is evidence in the literature that improved team work is associated with reduced mortality.[27] In our study, it was determined that the mean scores of the nurses' PSCS "employee behavior" subscale was in second place (2.83±0.56). The mean score for this subscale was 2.99 in the study

Table 2. Patient safety training status of the nurses (n=130)

Characteristics		n	%
Patient safety training status	Trained	79	60.8
	Not trained	51	39.2
Opinions on patient safety training sufficiency	No answer	6	4.6
	Sufficient	31	23.9
	Insufficient	93	71.5
Total		130	100.0

Table 3. Patient safety training subjects that nurses need (n=130)

Subjects	Education needs	n	%
Identifying patients correctly	No	107	82.3
	Yes	23	17.7
Safe drug application	No	87	66.9
	Yes	43	33.1
Transfusion safety	No	95	73.1
	Yes	35	26.9
Safe surgical applications	No	91	70.0
	Yes	39	30.0
Reducing the risk resulting from falls	No	112	86.2
	Yes	18	13.8
Effective communication	No	100	76.9
	Yes	30	23.1
Radiation safety	No	100	76.9
	Yes	30	23.1
Medical devices safety	No	86	66.2
	Yes	44	33.8
Total		130	100.0

of Yolcu et al.[20], and 2.80±0.58 in the study of Rızalar et al.[13], and these results are similar to our findings. Unlike our findings, in a patient safety culture study conducted by Klemenc-Ketis et al.[27], it was determined that the quality of team collaboration and communication was perceived by members of the health team as high. In our study, nurses received one of the highest scores from the "employee behavior" subscale. This finding indicated that nurses could provide an important contribution to patient safety culture as employees.

Training on patient safety is important in the prevention of mistakes and the improvement of patient safety Yolcu et al.[20]. In our study, it was determined that the "employee training" subscale was the third most important among the PSCS averages of the nurses (2.83±0.59). The mean score of this subscale was determined to be 2.6±0.37 in the study of Yolcu et al.[20], and 2.59±0.73 in the research of Rızalar et al.[13]. It was found that the average score obtained in our study was higher than these other scores. In the present study, it was determined that

Table 4. Score means and standard deviations of nurses' PSCS and subscales (n=130)

PSCS subscales	Numbers of items	Mean	Standard deviation
Management and leadership	17	2.81	0.50
Employee trainings	7	2.83	0.59
Unexpected incident and error reporting	5	2.68	0.54
Care environment	8	2.88	0.54
Employee behavior	14	2.83	0.56
PSCS total	**51**	**2.82**	**0.44**

PSCS: Patient Safety Culture scale.

more than half of the nurses (60.8%) received in-service training on patient safety. Similarly, in the study by Yilmaz and Goris[11], 69.6% of nurses were found to have received patient safety training as part of in-service training programs. A large number of nurses who participated in our study stated that their training for patient safety was inadequate. The nurses indicated that they needed training in the areas of radiation safety, medical device safety, safe drug applications, safe surgical applications, transfusion safety, effective communication, correct identification of the patient, and the reduction of the risk of falling. This finding is important in terms of showing the awareness of nurses about their own training needs. Continuous training on patient safety for all healthcare professionals is important for the establishment of patient safety culture in institutions. These findings obtained from our study emphasize the importance of regular training on patient safety to be carried out in institutions and the importance of determining the needs of nurses to prepare programs in this direction.

Managers and leaders should take the lead in measuring patient safety culture perceptions and attitudes, and pay attention to these outcomes in order to determine areas for improvement and the concerns of employees.[13] In our study, it was determined that the mean score of the nurses regarding the subscale of PSCS "management and leadership" was ranked in fourth place (2.81±0.50). The mean score for this subscale was determined to be 2.99±0.37 in the study of Yolcu et al.[20] and 2.62±0.49 in the research by Rızalar et al.[13]. Unlike our findings, in a study conducted by Hemmat et al.[28] in Iran, "expectations and actions of the managers upon patient safety" was the highest patient safety

Table 5. Comparison of mean PSCS scores and in-service education status of the nurses

Scales	In-service education	n	Mean	U	p
Management and leadership	No	51	53.25	1390.00	0.003*
	Yes	79	73.41	-	-
Employee training	No	51	58.90	1678.00	0.103
	Yes	79	69.76	-	-
Unexpected incident and error reporting	No	51	60.25	1746.50	0.195
	Yes	79	68.89	-	-
Care environment	No	51	57.31	1597.00	0.038*
	Yes	79	70.78	-	-
Employee behavior	No	51	56.11	1535.50	0.021*
	Yes	79	71.56	-	-
PSCS total	No	51	53.09	1381.50	0.003*
	Yes	79	73.51	-	-

*p<0.05. PSCS: Patient Safety Culture scale.

subscale. In our study, the "management and leadership" subscale mean score was not at the desired level. According to this result, it could be said that nursing managers should make more effort to support the practices of patient safety culture.

Patient safety culture is the basis for the prevention and correction of errors.[11] However, in our study, it was determined that the lowest score given by the nurses from the PSCS was in the "unexpected incident and error reporting" subscale. Similar findings were obtained in the "unexpected incident and error reporting" subscale in similar studies using PSCS.[13,20,22,23] Yolcu et al.[20], 2.99±0.39 and Rızalar et al.[13], 2.58±0.69, expressed that the "unexpected incident and error reporting" rate was low, which is in parallel with results from other studies conducted with different scales. It is believed that employees fear that they will be punished, excluded or negatively affected in their careers so they avoid reporting unexpected incidents and errors.[12,26,29,30,31,32] In this regard, in the study by Yilmaz and Goris[11], the "non-punitive response against errors" was identified as the lowest subscale. Reporting unexpected "incidents and errors" is aimed at forming awareness in the institution, and to develop a system which will prevent all possible risks, focus on solutions to reduce risks and to prevent medical errors and adverse events.[11,33] In this study, the mean PSCS scores of the nurses and subscales and their age and gender groups, education status, departments, and occupational experience were compared, but there was no statistically significant difference between these variables and the mean scores of PSCS ($p>0.05$). In a study using another PSCS in the operating rooms of seven health institutions in Tunisia, it was determined that there was no relationship between the scales and the ages, genders, or professional experiences of the participants.[34]

It was found that the total scores of the PSCS, the "management and leadership", "care environment" and "employee behavior" subscales of those nurses who had received in-service training were higher than those of the non-trained nurses ($p<0.05$). In the study of Rızalar et al.[13], it was determined that the average of the subscale scores of those nurses who had received training in certain subjects were higher than those who had not. In Karaca and Arslan's[22] study, the nurses' mean score of PSCS and its subscales were found to be statistically significant in all subscales other than the "care and technology" subscale in terms of their patient safety training. In the study of Ertürk et al.[23], it was determined that the scores of those individuals who had received patient safety training was not statistically significantly higher in all the subscales and the difference between the groups was higher than the total score. It is important for nurses to gain competence in order to prevent errors and improve patient safety. This competence, which is acquired during the training period, should be supported by orientation programs in the field of work and continuous training. The training needs of employees should be determined and training programs should be planned accordingly.

Study Limitations

This study has one limitation. It was carried out only in a university hospital. The results of this study can only be generalized to this hospital, and not to other hospitals and clinics.

CONCLUSION

In conclusion, in this study, it was determined that the nurses' PSCS scores were above the average level. The lowest mean score was in the "unexpected incident and error reporting" subscale, and the highest mean score was in the "care environment" subscale. The total scores of PSCS, "management and leadership", "care environment" and "employee behavior" subscales of those nurses who had received in-service education were found to be higher than those who had not received training. It is important to ensure patient safety culture in all institutions. Therefore, based on the findings of this study, to assess the patient safety culture of all employees in the institution, to determine any insufficiencies, to monitor any changes, and to carry out an effective error reporting system which allows employees to report medical errors without fear, it is recommended to repeat the patient safety culture measurements and to provide continuous training on patient safety and to raise the awareness of all employees by emphasizing the necessity for patient safety in these training sessions.

MAIN POINTS

- In this study, it was determined that the nurses' PSCS scores were above the average level.
- The highest score average was found in the "care environment" subscale and the lowest score average was found in the "unexpected incident and error reporting" subscale.
- The positive "care environment" subscale result suggests that the institutional care environment in which this research was conducted is effective in ensuring patient safety.

ETHICS

Ethics Committee Approval: Approval for this scientific research by the ethics evaluation board of the university (approval number: YDU/2016/42-348, date: 22.12.2016).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.Ö.K., B.T.D., Design: Ş.Ö.K., Supervision: N.B., Ü.D.Y., Fundings: B.T.D., Materials: B.T.D., N.A., Data Collection and/or Processing: B.T.D., N.A., Analysis and/or Interpretation: Ş.Ö.K., B.T.D., N.B., Ü.D.Y., Literature Search: Ş.Ö.K., B.T.D., N.B., Writing: Ş.Ö.K., B.T.D., N.B., Critical Review: Ş.Ö.K., N.B., Ü.D.Y.

DISCLOSURES

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

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RESEARCH ARTICLE

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Knowledge, Attitudes and Practices of Pediatric Nurses in Turkey Towards the Use of Physical Restraints

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Abstract

BACKGROUND/AIMS: The use of physical restraint in children holds greater importance compared to adults due to the fact that children cannot express themselves. This research, taking into account the important role of pediatric nurses in ensuring patient rights and safety, was conducted as a descriptive and cross-sectional study to determine the knowledge, attitudes, and practices regarding the use of physical restraint.

MATERIALS AND METHODS: The study population consisted of 152 nurses working in the pediatric clinics of a university and a public hospital. The participant data were collected using the "Levels of Knowledge, Attitudes and Practices of Staff Regarding Physical Restraints Questionnaire". The data were analyzed using SPSS, and percentage, Mann-Whitney U and Kruskal-Wallis analyses were performed.

RESULTS: It was observed that all of the pediatric nurses who participated in this study used physical restraints. The most common type of physical restraints were wrist restraints (95.4%) and the reason for physical restraints was to prevent the agitated child from harming themselves and/or others (93.4%). It was observed that the knowledge, attitudes and practices regarding the use of physical restraint were affected by whether the nurses had received any previous education on physical restraints and which unit they worked in ($p<0.05$).

CONCLUSION: The results of this study suggest that pediatric nurses in Turkey need education and specialist counseling regarding physical restraints and relevant protocols must be established by health organizations.

Keywords: Physical restraints, pediatric nurses, knowledge, attitudes, practices

INTRODUCTION

Physical restraining is the use of physical, chemical or mechanical tools and devices which allow the restriction of a part of a demented, agitated or confused patient's body to control/restrain the patient's physical movements in order to prevent the patient from harming and/or injuring themselves, and to ensure the safe treatment of the patient.[1,2] The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) defines physical restraint as the "use of physical restraints for the purpose of controlling the actions of a person, without the consent of the person".[3,4] Physical restraint is generally used for pediatric patients, patients in intensive care units and patients over 65 years of age.[5] Physical restraint is mostly used in cases where the patient exhibits physically harmful behavior and alternative methods are insufficient to protect the patient.[6,7] There is often a need to completely restrain children for special procedures.[8] In this respect, physical restraint is used to control movement with the aim of providing appropriate posture, reducing the risk of falling, preventing the removal of critical equipment, reducing the risk of harm to themselves or others and facilitating the application of medical treatments in pediatric patients.[4,8-12] In addition, physical fixation application in the child is frequently used in cases of staff shortage and when the child needs urgent medical interventions.[7]

Physical restraint applications are perceived as beneficial for the patient, however, it is highly important to evaluate the advantages and disadvantages of physical restraints especially in pediatric patients who

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are unable to express themselves. In the literature, the prolonged and uncontrolled use of physical restraints has been associated with muscle weakness, urinary and fecal incontinence, pressure sores and related infections, insomnia, agitation, confusion, fear, depression, decreased self-confidence and self-respect, deteriorated body image, lack of sensation and negative consequences such as death due to asphyxia.[5,13,14] Health care providers need to identify opportunities to decrease the risks associated with the use of restraints through preventive strategies, innovative alternatives and procedural improvements in order to help focus on the pediatric patients overall well-being, health and safety.[8]

It is known that there are differences in restraint standards between different countries.[15-17] However, according to the JCAHO standards, the use of physical restraint should be initiated by professionals upon the order of a physician, and nurses are entitled to use physical restraints only in the absence of the physician and provided that a written order is obtained within 12 hours.[18] In Turkey, it is necessary to obtain a physician order and informed consent given by the patient or surrogate in order to use physical restraint.[3,19] In recent years, there has been a significant increase in studies which aimed to determine the frequency of application, levels of knowledge and attitudes of nurses and to minimize the use of physical restraint.[20-22] However, there are a limited number of studies in pediatric nurses in Turkey and developing countries.[10] The use of physical restraint in children holds greater importance compared to adults due to the fact that children cannot express themselves. Therefore, taking into account the important role of nurses in providing patient rights and safety, this topic holds great importance since physical restraint often causes harm to pediatric patients rather than preventing it and it is a critical issue of human rights with regard to physical, psychological, social and legal aspects.

This study was carried out to determine the knowledge, attitudes and practices of pediatric nurses with regard to the use of restraints and their associated factors.

MATERIALS AND METHODS

Type of study: This research was conducted as a descriptive and cross-sectional study.

Study place and features: This study was carried out on pediatric nurses working in a university hospital and a public hospital located in the north of Turkey.

Study population-sample: Data collection was conducted between May and June 2018. The number of nurses in the population was 228, while the number of nurses in the sample (those with an experience of at least one year and those not working in polyclinics) was 191 in total. The study was completed with 152 nurses (66% rate of participation) excluding those who were on leave, those who did not fill in the questionnaire completely and those who did not agree to participate in this study.

Data collection tools: The data were collected using the "Information form" developed by the authors and the "Levels of Knowledge, Attitudes and Practices of Staff Regarding Physical Restraints Questionnaire".[23] A face-to-face questionnaire was conducted. The questionnaires were filled in with the nurses in their rest-room so that they would not be affected by each other.

Personal information form: This form was designed by the author according to the literature. It consisted of a total of 13 questions on the socio-demographic and occupational characteristics, previous educational background on physical restraint, application and reasons for physical restraint among the nurses.

Levels of Knowledge, Attitudes and Practices of Staff Regarding Physical Restraints Questionnaire: The Levels of Knowledge, Attitudes and Practices of Staff Regarding Physical Restraints Questionnaire was improved by Suen[24] in 1999 and the test-retest total correlation co-efficient of the original scale was determined to be 0.85-0.99. The scale was adapted into Turkish by Kaya et al.[23] with a test-retest value of 0.88-0.90 and a Cronbach's alpha co-efficient of 0.69. In this study, the Cronbach's alpha co-efficient was determined to be 0.64. This scale was used in different previous studies whose samples included nurses working in pediatric clinics.[4,5,25] The scale was adapted into Turkish by the authors and includes three sections. The first section consists of 11 items with 10 correct answers (true) and 1 wrong answer (false) to the questions. This section aims to measure the knowledge of nurses on the use of physical restraint. Correct responses are given 1 point, whereas incorrect responses are given 0 points. The score limits of this section range between 0 and 11, with higher scores indicating higher levels of knowledge. The second section is a 4-point Likert-type scale consisting of 12 items which measure the attitudes of nurses toward the use of physical restraints, in which "*I definitely agree*" is evaluated as 4 points: "*I agree*" as 3 points, "*I disagree*" as 2 points and "*I absolutely disagree*" as 1 point. The score limits of this section range between 12 and 48, with high scores indicating positive and lower scores indicating negative attitudes. The third section consists of 14 items which evaluate the use of physical restraints among nurses. In this section, item 10 is a negative item and is evaluated in reverse order compared to the rest of the items. This section was designed as a 3-point Likert scale, in which "never" is evaluated as 1 point, "sometimes" as 2 points and "always" as 3 points. Scores range between 14 and 42 and higher scores indicate an excellent application of physical restraints practices whereas lower scores indicate unsuitable practices. In this study, the Cronbach's alpha value was determined to be 0.76 with the knowledge subscale value of $\dot{\alpha}$=0.59, the attitude subscale value of $\dot{\alpha}$=0.77 and the practice subscale value of $\dot{\alpha}$=0.84.[23]

Ethical consideration: The data collection was initiated after obtaining the approval of the Ondokuz Mayıs University Ethics Committee (approval number: B.30.2.ODM.0.20.08/1563-1620, date: 30.04.2018). The participants signed written informed consent forms before completing the survey. They voluntarily and anonymously participated in this study, and there were no actions taken against non-participation.

Statistical Analysis

The data were analyzed using the SPSS software version 23. Descriptive statistics included number, percentage, mean, standard deviation, and median. Inferential statistics for normally distributed data included parametrical tests (independent two-sample t-test, One-Way analysis of variance and Tukey's test), and for non-normally distributed data included non-parametric tests (Mann-Whitney U, Kruskal-Wallis H test, Tamhane's T^2 test).

RESULTS

It was determined that the majority of the nurses were in the 31-40 age group, female, married, had a bachelor's degree and a professional experience of 1-10 years and, finally, one third of them worked mainly in maternity departments, and one quarter worked mainly in pediatric intensive care units (Table 1).

The study results demonstrated that all of the pediatric nurses who participated in this study (100%) used physical restraints. In addition, 45.4% of the nurses stated that they had previously participated in an education program on physical restraints and 71.7% said that both nurses and physicians were entitled to decide on the use of physical restraints. It was found that the most common types of restraint used by the nurses were wrist restraints and ankle restraints. When questioned about the factors as to why they used physical restraints, the most significantly reported reasons were to prevent the agitated children from harming themselves and/or others, to prevent the child from pulling at the attached medical devices, to prevent falls and to manage pediatric patients with altered consciousness. A high proportion of the nurses stated that physical restraint applications should be recorded, while all of them stated that the child who underwent physical restraint should be monitored. A small number of the pediatric nurses stated that they observed complications associated with the use of physical restraints.

Table 1. Descriptive characteristics of the nurses (n=152)

Characteristics	Number (n)	Percentage (%)
Age (years): 35.03±7.09 (minimum: 23-maximum: 55)		
20-30-year olds	34	22.4
31-40-year olds	78	51.3
40 years and older	40	26.3
Gender		
Female	149	98.0
Male	3	2.0
Marital status		
Married	120	78.9
Single	32	21.1
Educational background		
High school	7	4.6
Associate degree	27	17.8
Graduate degree	109	71.7
Post graduate degree	9	5.9
Length of professional experience		
1-10 years	73	48.0
11-20 years	51	33.6
21-30 years	28	18.4
Current unit		
Maternity unit	53	34.9
Pediatric intensive care unit	37	24.3
General pediatrics	33	21.7
Pediatric emergency care	16	10.5
Surgical unit	13	8.6
Total	152	100.00

When the nurses were asked what measures they took to minimize the use of physical restraints, it was determined that the majority of the nurses raised bed rails and ensured the child was accompanied by the mother and they tried to calm the child down by talking to them. Only a small number of the nurses stated that they obtained permission from the family before using physical restraints, with nearly all of them reporting that they recorded the procedure (Table 2).

Among the nurses, the mean scores regarding the use of physical restraints were determined as follows; the mean knowledge level score was 8.37±1.02, the mean attitude score was 20.14±3.90 and the mean practice score was 33.91±3.13 (Table 3).

Age, marital status, gender, educational background and length of professional experience were not statistically correlated with the

Table 2. Nurses' attitudes regarding physical restraints (n=152)

	Yes, n (%)	No, n (%)
Application of physical restraint	152 (100)	-
Obtaining information about physical restraint during nursing education	69 (45.4)	83 (54.6)
The authority to use physical restraint		
Nurse	6 (3.9)	146 (96.1)
Physician	37 (24.3)	115 (75.7)
Both	109 (71.7)	43 (28.3)
Most common type of physical restraint		
Wrist restraints	145 (95.4)	7 (4.6)
Ankle restraints	131(86.2)	21 (13.8)
Use of physical force to prevent harm to the agitated patient	27 (17.8)	125 (82.2)
Hand and ankle restraints in addition to chest or waist restraints to the bed at the same time	16 (10.5)	136 (89.5)
Chest and waist restraints	7 (4.6)	145 (95.4)
Reasons for physical restraint in pediatric patients		
To prevent agitated patients from harming themselves and/or others	142 (93.4)	10 (6.6)
To prevent pediatric patients from removing attached medical devices	132 (86.8)	20 (13.2)
To prevent falling off the bed	129 (84.9)	23 (15.1)
Altered state of consciousness	113 (74.3)	39 (25.7)
To carry out medical treatment	91 (59.9)	61 (40.1)
To compensate for insufficient staff	20 (13.2)	132 (86.8)
Complications associated with physical restraints	12 (7.9)	140 (92.1)
Methods to minimize the use of physical restraints		
Raise bed rails	141 (92.8)	11 (7.2)
Ensure the child is accompanied by the mother	147 (96.7)	5 (3.3)
Calm the child down by talking	118 (77.6)	34 (22.4)
Allow the child to play games	104 (68.4)	48 (31.6)
Administer drugs	68 (44.7)	84 (55.3)
Family consent	6 (3.9)	146 (96.1)
Written record of physical restraint application	146 (96.1)	6 (3.9)

knowledge levels, attitudes and practice scores of the nurses regarding physical restraints (p>0.05). Knowledge on physical restraints and the working units were significantly correlated with the mean knowledge and attitudes scores (p<0.05). Moreover, there was a statistically significant correlation between knowledge and previous education programs on physical restraints and the mean attitude scores (p<0.05), whereas no statistically significant correlation was found between the mean practice scores (p>0.05) (Table 4).

DISCUSSION

In this study, we aimed to explore the knowledge and practices of pediatric nurses about physical restraint, and our findings show that all of the nurses used physical restraint (Table 2). International and national studies have also revealed that the use of physical restraint in pediatrics and other fields is highly common in clinical settings, which is also consistent with our study results.[5,6,10,22,26,27]

Our study results showed that almost half of the pediatric nurses had received previous education on physical restraint (Table 2). In fact, the subject of physical restraint and application is included in both the nursing undergraduate education and the clinical training conducted in the hospital. However, the other half stated that they had not received such training. Other current studies have noted that nurses have insufficient education with respect to physical restraint.[9,10,14,16,20] However, it is also emphasized that the use of physical restraint should only be preferred after the elimination of alternative methods in order to ensure patient safety and that nurses should be educated and experienced in order to ensure that physical restrains are applied safely.[1,3,28,29]

The participating nurses stated that they mostly used physical restraints to prevent agitated children from hurting themselves and/or others, to prevent the removal of attached medical devices, and to prevent children from falling off the bed (Table 2). Pediatric nurses are more likely to use restraints depending on the need to ensure the security of pediatric patients and to prevent adverse sequelae.[10,30] In addition, nurses working in pediatric clinics stated that the need to use restraint was more related to the application of interventions (such as nasogastric tube insertion, Lumber puncture, IV catheter insertion) rather than the individual care needs of the child,[7,22,30] which was consistent with other studies in the literature.

The majority of nurses in this study stated that they raised the bed rails, ensured that the child was accompanied by the mother, calmed the child down by talking to them and allowed the child to play in order to minimize the use of physical restraints (Table 2). Previous studies have noted that physical restraints should be applied carefully and only when necessary and that alternative methods should always be considered in order to reduce the negative effects on children and their family, although the use of physical restraint is frequently required in many pediatric cases.[22,29] It is known that physical restraint is mostly used for medical procedures in pediatric clinics, therefore, it is stated that supporting a child and their family in medical interventions before, during and after the restraint procedure (e.g. lumber puncture) may reduce the need for physical restraint.[7,22,31] Methods such as the presence of the family during medical interventions applied on the child, using distractive methods (breathing exercises, listening to music, watching film, etc.), ensuring that the child is in a comfortable position during invasive procedures, using oral or local analgesics before the procedure

Table 3. The mean subscale scores of the participants in the Scale of Nurses Using Physical Restraint (n=152)

	Mean ± SD	Min.-max.	Median
Nurses' knowledge level regarding physical restraints	8.37±1.02	5-9	9
Nurses' attitudes regarding physical restraints	20.14±3.90	7-28	20
Nurses' practices regarding physical restraints	33.91±3.13	16-36	35

SD: standard deviation, Min.: minimum, Max.: maximum.

Table 4. Knowledge, attitudes and practice scores regarding the use of physical restraints based on any previous education programs on physical restraints

	Nurses' knowledge level regarding physical restraints		Nurses' attitudes regarding physical restraints		Nurses' practices regarding physical restraints		
	Mean ± SD/median (min.-max.)	Test statistics, p-value	Mean ± SD/median (min.-max.)	Test statistics, p-value	Mean ± SD/median (min.-max.)		Test statistics, p-value
Current unit							
Newborn intensive care unit	8.60±7.43/9 (7-9)	KW=8.954 **0.030**	20.75±3.38	F=4.42 **0.002**	34.77±1.76/35 (24-36)		KW=7.695 **0.042**
Pediatric intensive care unit	8.56±1.14/9 (6-9)		18.56±3.61		34.60±1.14/35 (24-36)		
General pediatric service	8.30±0.91/8 (6-9)		20.18±3.25		34.37±2.65/34 (32-36)		
Pediatric emergency unit	8.03±1.14/8 (7-9)		18.25±3.08		33.13±3.25/34 (25-36)		
Pediatric surgery unit	8.08±1.18/8 (6-9)		17.53±3.64		32.46±5.26/34 (16-24)		
Obtaining information about physical restraint during nursing education							
Yes	8 (6-9)	U=1956.000 **0.001**	18 (7-25)		U=2313.000 **0.040**	35 (25-36)	U=2723.500 0.593
No	9 (5-9)		20 (9-28)			35 (16-36)	

KW: Kruskal-Wallis tests, U: Mann-Whitney U test, min.: minimum, max.: maximum, F: One-Way analysis of variance and Tukey's test.

and having an experienced health team perform the invasive procedure decrease the need to use physical restraints.[13,30] It is necessary to reward or praise the child after a medical procedure, accompany the child until calm if he/she is upset and explain to the child and their parents why it is necessary to use physical restraint.[22,31] This information suggests that the use of alternative methods to physical restraint should be promoted and expanded.

In our study, only one quarter of the nurses acknowledged that the physician was the true authority on deciding whether to use physical restraint (Table 2). However, according to the JCAHO standards, the use of physical restraint should be initiated by professionals only upon the order of a physician. Additionally, nurses are entitled to use physical restraints only in the absence of a physician provided that a written order is obtained within 12 hours.[32] In Turkey, physical restraint can only be used upon a physician's order according to the instructions published by the Ministry of Health on the care of patients under restriction.[19] Previous studies conducted in Turkey have determined that nurses use physical restraints independently without obtaining a physician's order.[9-11,14,25,33] According to several international studies, nurses in Singapore used physical restraints without a physician's order, nurses in Hong Kong tended to decide on the use of physical restraints, and the use of physical restraints could be only authorized by physicians in Canada.[20,34] The comparison of Turkey with other countries show that there are some differences in the application of physical restraints, which may be due to different policies related to public health between the countries.

This study shows that none of the nurses obtained permission from the family for the use of physical restraints (Table 2). Studies conducted in Turkey have revealed that there is a serious deficiency in obtaining permission from the family in cases where physical restraint is required.[5,10,11,13] International studies have demonstrated that nurses frequently obtain permission from the families and even the children at times.[6,7,21,30,35] According to some recent studies, the use of physical restraint in children without their consent should be considered as a last resort.[31,35] The results of these studies are thought to be related to the insufficient knowledge of nurses regarding procedures and their responsibilities in terms of the physical restraint practices in our country and the ineffective use of the consent form in hospitals. In Turkey, it seems apparent that legal arrangements should be made on this issue.

In this study, most of the nurses reported recording physical restraint applications (Table 2). It is unclear whether patients should be monitored closely considering the physical, psychological and social impact which physical restraints may cause. A previous study found it important to evaluate the patients' responses after undergoing physical restraints, to monitor the patient closely and to record these results properly.[28] The results of this study showed that the nurses did not record the use of physical restraints, some did not deem it necessary,[3] and some nurses were aware of the importance of keeping records, and they often refrained from doing so in practice.[23,25] Our findings contradict the literature. Considering the role and importance of maintaining records and reports in nursing care, it appears that the necessary training should be carried out to improve the nurses' knowledge, attitudes and practices on such topics.

The mean scores of knowledge, attitudes and practice scores related to physical restraint were found to be quite favorable among the nurses, which is thought to be correlated with their high quality of nursing care (Table 3). The reason why the nurses exhibited better knowledge, attitudes and practices about physical restraint was attributed to the fact that pediatric areas include more invasive procedures, which require the use of physical restraints more frequently compared to the other clinics.[4,11,28]

This study's findings demonstrated that nurses working in neonatal and pediatric intensive care units have greater knowledge and better attitudes compared to those nurses working in other pediatric clinics (Table 4). A relevant domestic study revealed that the level of knowledge and attitudes is moderate among the pediatric intensive care nurses regarding the use of physical restraints, however they exhibited better behavior. In the same study, it was found that the knowledge and attitudes of nurses working in the service for older children were more positive than the intensive care nurses but there was no difference between their behaviors.[4] Again, in Turkey, another review of the nurses working in the pediatric surgery service demonstrated that most perceived physical restraint as a natural part of treatment and care, and it is mostly used to ensure the safety of the child, however, approximately half of the nurses used alternative methods in order to reduce the use of physical restraint.[13] The pediatric oncology nurses stated that the use of physical restraint is of great benefit when the procedure is managed successfully, however, it should be applied carefully and alternative methods should be considered at all times even when the use of physical restraint is necessary.[29]

In this study, it was found that those nurses who had been trained with regards to physical restraint during their undergraduate education had more information and more positive attitudes about the application of physical restraints, but this did not affect practices about the use of physical restraints. Recent studies have found that having attended training was not related to knowledge, attitude and practices among pediatric nurses, whereas the rate of physical restraint use was even higher among those nurses who had received in-service training compared to the others.[4,10] Performance improvement processes through the education of staff allow for ongoing opportunities to improve care and reduce the risks associated with restraint use.[12]

Study Limitations

The limitations of this study are the facts that it was carried out in only one region of the country and it was based on nurses' self-reporting.

CONCLUSION

This study demonstrated that all of the participating pediatric nurses opted for physical restraint, with the most common type of restraint being extremity, while the most common reason for the use of restraint was to prevent pediatric patients from harming themselves and pulling at medical devices. It was observed that the nurses generally had a favorable level of knowledge, positive attitude and suitable behavior, whereas those working in pediatric intensive care units and neonatal units exhibited higher levels of knowledge, attitude and behavior, in particular. It was found that those nurses who had been trained about physical restraint during their undergraduate education had more

information and more positive attitudes regarding the application of physical restraints, but this did not affect their practices about the use of physical restraints. In addition, it was noted that nurses tried some alternative methods to reduce the use of physical restraints, but they did not seek approval from physicians prior to the application of physical restraint. Again, in the study, it was observed that the nurses did not make an attempt to obtain informed consent from children or their parents for the use of physical restraints.

This study highlights the lack of education and specialist counseling regarding physical restraint among pediatric nurses in Turkey, and the necessity to follow the necessary protocols established by health organizations. In this regard, it is necessary that this topic is widely integrated into the Turkish nursing curriculum, and that regular in-service training programs are carried out, particularly for pediatric nurses, in order to inform and educate them. Given the fact that physical restraints are more commonly used in pediatric care units, further studies are needed to provide a basis for evidence-based practices, to develop protocols and to emphasize the importance of this subject. Therefore, additional studies on the use of physical restraint by pediatric nurses are recommended.

MAIN POINTS

- This study highlights the lack of education and specialist counseling regarding physical restraint among pediatric nurses in Turkey, and the necessity to follow the necessary protocols established by health organizations.
- This study may help to raise awareness among pediatric nurses regarding the ethical aspects of physical restraint applications and to raise awareness regarding the necessity in this regard.
- It is recommended to develop new approaches in order to reduce the use of physical restraint and its associated complications in children.

ETHICS

Ethics Committee Approval: The data collection was initiated after obtaining the approval of the Ondokuz Mayıs University Ethics Committee (approval number: B.30.2.ODM.0.20.08/1563-1620, date: 30.04.2018).

Informed Consent: The participants signed written informed consent forms before completing the survey.

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RESEARCH ARTICLE

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Turkish Expectant Fathers' Experiences of Sexual Life During Pregnancy: A Qualitative Study

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Abstract

BACKGROUND/AIMS: The feelings and thoughts on sexuality and sexual activity of expectant fathers, similar to mothers during pregnancy, are influenced by many factors. Therefore, this qualitative study was conducted to investigate Turkish expectant fathers' experiences regarding their sexual life during pregnancy.

MATERIALS AND METHODS: The sample of the study consisted of 29 expectant fathers. The data of this study were collected using a semi-structured individual in-depth interview form and a personal information form. Researchers prepared the forms based on the relevant literature. The data were analyzed using content analysis.

RESULTS: Two main themes were developed as a result of this study. The first theme, *"Feelings and thoughts on sexuality",* revealed that sexuality/sexual activity was very important for expectant fathers, however, this was not communicated between the spouses, and expectant fathers did not want to talk about sexuality. The other theme, *"Sexual life during pregnancy",* showed that pregnancy affected sexual life, and it strengthened the marriage and the bonds between spouses. The themes also revealed that the expectant mothers were disturbed by their changing body images and feared their husbands engaging in extramarital relationships, and that sexual intercourse might become a dull duty during pregnancy.

CONCLUSION: In accordance with these results, researchers recommend creating a service model which includes expectant fathers in order to provide couples with an information service through an integrative approach.

Keywords: Pregnancy, expectant fathers, sexual life, experiences, nursing

INTRODUCTION

According to the World Health Organization, sexuality is defined as the combination of physical, emotional, intellectual and social aspects of personality, communication, and love-enhancing effects.[1] The expression of sexuality, which starts in intrauterine life and continues until death, differs in every period of life. Human sexuality is a multidimensional phenomenon developing throughout life, and it is influenced by psychological, physiological and socio-cultural factors.[2]

Pregnancy is an important life experience which affects sexuality. Pregnancy, having an important place in women's lives, is a transition from one psychological state to another: from being a couple to becoming a family.[2] It is a process during which many changes

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and feelings occur, which are affected by biological, psychological and social factors. Accordingly, it significantly affects the sexual behaviors of the couple.[3-5]

Although in normal conditions pregnancy occurs because of sexual intercourse, sexual life is still a taboo subject in certain societies. Thus, couples do not get enough counseling from health professionals during pregnancy and the sexuality of the couple is interrupted.[6] In the literature, the usual reasons for the interruption of sexual activity during pregnancy are seen to be worries about the risks of damaging the fetus, miscarriage, infection, early delivery and preterm membrane rupture development.[7-10]

The minimum follow-up is carried out four times in the prenatal period in Turkey.[11] During these follow-ups, the main focus is on the physical health of pregnant women but not on their sexual lives. In addition, expectant fathers are not provided with any service during this period and their informational needs are not met.[12] Therefore, couples have a misconception about their sexual life. Culture and religion are also particularly influential on such an issue in Turkey as sexual intercourse during pregnancy may be perceived as shameful, prohibited and sinful in Turkish culture.[13] In addition, emotional changes such as ambivalence, refraining from having sexual intercourse with one's spouse, fear of damaging the fetus, anxiety, and depression may occur in expectant fathers during pregnancy. All these factors negatively affect the sexual lives of couples during pregnancy.[2] Therefore, couples should try to maintain their relationship in a healthy way in order to develop their mutual emotional bond and close physical attraction, to achieve their sexual satisfaction, and to satisfy the sexual needs of each other.[14]

During pregnancy, couples often interrupt sexual activity for various reasons and are reluctant to ask questions about their sexual life. Thus, pregnant women and their spouses who experience problems in maintaining their sex life during pregnancy may need professional support. Especially, since nurse are close to the pregnant women and their spouses, they should try to consult with the couple in order to help them adapt to this new situation. Furthermore, they should try to eliminate the concerns, worries, and misconceptions of the expectant couple regarding sex during pregnancy.[2]

Despite, the existence of many studies on pregnant women's sex lives in the literature,[3-10] there are not enough scientific studies on the sex lives of expectant fathers. This situation was one of the most important reasons which prompted the researchers to conduct this study.[15-17]

The present paper is an attempt to provide answers to the following questions:

1. Does pregnancy affect the sexual experiences of expectant fathers?
2. Do expectant fathers experience sexual problems and changes during pregnancy?
3. How do the expectant fathers perceive sexuality?

MATERIALS AND METHODS

Study Design

This qualitative study was conducted to investigate Turkish expectant fathers' experiences of their sexual life during pregnancy.

Selection and Description of Participants

Expectant fathers attending a university hospital's obstetrics outpatient clinic between August 25th and October 18th, 2017, with their wives, participated in this study. A purpose-oriented sample selection method was used in this study. The sample selection approach utilized in our study required the data collection process to continue until the concepts and processes that are able to answer the research questions begin to repeat themselves (saturation point).[18] The researchers concluded that the saturation point was attained when the sample reached 29 individuals who agreed to participate in this study.

Data Collection Procedures

The data collection form included two sections. The first section consisted of questions regarding the socio-demographic characteristics of the expectant fathers, which are age, profession, education, longest-lived place of residence, age disparity between the husband and his wife, their number of children and the gestational week of the wife. The second section included the "*semi-structured individual in-depth interview form*", which was prepared in order to determine the feelings, thoughts, and experiences of the expectant fathers in relation to their sexual lives during pregnancy.[3-5,15-17]

The following four questions were included in the individual in-depth interview form:

1. How was your relationship with your wife before; and how is it now during pregnancy?
2. Could you explain your feelings and thoughts about your sexual life before and during pregnancy?
3. Do you think that pregnancy has affected your sexual life? (Positively/negatively).
4. Could you explain yours and your wife's opinions and experiences about receiving information/counseling regarding sexuality during pregnancy?

After receiving the opinions of two qualitative research experts, the semi-structured individual in-depth interview questionnaire was put into its final form. Following this, a pilot application of the questionnaire was carried out with five expectant fathers to assess the usability of the semi-structured individual in-depth interview questionnaire. No modifications were made to the questionnaire after the pilot application.

Expectant fathers who came to the outpatient clinic with their wives were invited to individual in-depth interviews. When the pregnant women came to the outpatient clinic alone, they were informed about the participation of their husbands in the research, and their phone numbers were obtained. The purpose of this study was explained to those expectant fathers who accepted to participate in the study before starting. In addition, if there were any hesitations about the researchers or the study on the part of the expectant fathers, they were reminded of their opportunity to disclose their hesitations. They were requested to read and sign the "*informed consent*" and to fill in "*Personal Information forms*". Prior to the interview, the expectant fathers were assured of the confidentiality of all the information given by them. Face-to-face interviews were conducted with expectant fathers at a determined date and time in the investigator's office by

a researcher. Interviews were recorded with an audio recorder after obtaining permission from the expectant fathers. The investigator also took notes about the body language of the expectant fathers during the interviews, paying special attention to their gestures and mimics. Each interview lasted for approximately 60 minutes.

All procedures were approved by Mersin University Social Sciences Institutional Ethics Review Board (approval number: 2017/53) and Mersin University Health Research and Application Center (approval number: 41993462-774.001.0600000443843). In addition, all the participants signed informed consent forms.

Statistical Analysis

Within the analysis process of the data obtained through the semi-structured individual in-depth interviews, at first, the recordings of the interviews were transcribed and classified. The content analysis was carried out by the researchers by taking into consideration the prevalence of the comments in the answers given, the number of participants who made the same comment or used the same words. As for the qualitative analysis of the data transferred to the computer, researchers paid heed to what was meant to be said and the originality of the responses. The raw data were coded after being carefully read by the researchers. Themes were created by combining the coded data. The themes obtained were sent to the two above-mentioned experts who are experienced in the field of qualitative research. The content analysis was completed after receiving expert opinions. The data concerning the socio-demographic characteristics of the expectant fathers, as well as the gestational weeks of the spouses and probable problems during pregnancy were assessed through the SPSS, 20.0 (Chicago, Illinois, USA) package software in terms of mean, standard deviation, minimum and maximum values.

RESULTS

As presented in Table 1, the average age of expectant fathers was determined to be 33.5±5.1 years. The number of expectant fathers working as government employees was 18; 22 had at least a bachelor's degree, 16 lived in the province, the average age difference between them and their spouses was 4±3.4 years, 17 did not have a previous child. The average gestational week of their spouses was 26.3±10, and 25 had not had any problems during pregnancy.

The content was analyzed to determine the characteristics of the sexual life of expectant fathers during pregnancy. Two main themes and eight sub-themes were obtained (Table 2).

Theme 1. Feelings and Thoughts on Sexuality

1.1. The Significance of Sexuality for Expectant Fathers

All expectant fathers explained sexual activity as a vital need such as eating and drinking, a function that is necessary for reproduction, happiness, pleasure, satisfaction, and joy. The expectant fathers stated that sexual activity is an important and vital need in daily life and marriage, especially for men. The statement of one of the expectant fathers regarding the significance of sexual activity is quoted below:

"It is a necessity, a desire of the body, there is somehow a production in the body, especially in the male's, of course, you do not know what happens after that poison spreads to the body, though... I can say it is primarily a necessity." (#18, 30 years old, master's degree, expecting his first child).

"It is one of the basic elements such as food and water. It's quite a principal criterion for a man to feel manly. The impulse or the psychology behind reproduction, which is caused by hormones, is intended to make you feel normal. The word 'pleasure' simply means the joy of life." (#6, 36 years old, Master's degree, expecting his first child).

1.2. Feelings About Sexuality are not Communicated Between the Spouses

In the study, 17 expectant fathers reported that they did not talk with their spouses about their emotions since they thought that there was no problem concerning their sexual life during pregnancy. Below is the statement of an expectant father.

"We do not talk excessively about those subjects, but we do not worry about it. No, we did not talk on it at all, but this is a normal process, so we did not feel a need to talk." (#26, 27 years old, Bachelor's degree, expecting his second child).

1.3. Expectant Fathers do not Want to Talk About Sexuality

In the study, 9 expectant fathers said that they did not want to have any discussions regarding sexuality or their sexual life. Four expectant fathers stated that sexuality was considered forbidden and a "sinful matter" in society. The statements of two expectant fathers regarding this topic are as follows:

Table 1. Sociodemographic characteristics of the participants (n=29)

Sociodemographic characteristic			
	$\bar{X}$ ± SD	Minimum-Maximum	(n)
Age	33.5±5.1	22-43	29
Profession			
State employee	-	-	18
Craftsman	-	-	6
Worker	-	-	5
Education level			
Primary school	-	-	4
High school	-	-	3
University	-	-	22
Longest place of residence			
Village	-	-	5
District	-	-	8
Province	-	-	16
Age disparity between spouses	$\bar{X}$ ± SD	Minimum-Maximum	
	4±3.4	0-11	29
Status of having previous children			
Yes	-	-	12
No	-	-	17
Gestational week of the wife	$\bar{X}$ ± SD	Minimum-Maximum	
	26.3±10	10-40	29
Status of having any problems during pregnancy			
Yes	-	-	4
No	-	-	25

SD: standard deviation.

Table 2. Main-themes and sub-themes	
Theme 1. Feelings and thoughts on sexuality	**Theme 2. Sexual life during pregnancy**
1.1. The significance of sex for expectant fathers	2.1. Pregnancy may affect sexual life
1.2. Feelings about sexual lives are not communicated between the spouses	2.2. Pregnancy may strengthen the marriage and increase the bond between spouses
1.3. Expectant fathers do not want to talk about sexual lives	2.3. The effect of the changes of the body image on pregnant women and the fear of an extramarital affair
1.4. Expectant fathers are not willing to receive counseling on their sexual lives	2.4. Sexual intercourse may become just a duty during pregnancy

"I do not think that it (talking about sex/sexuality) is necessary. I mean, it is a private issue, we talk about (the health condition of) my (pregnant) wife." (#10, 37 years old, secondary school graduate, expecting his third child).

"In our society, religion is very important; we do not talk about the sexual and private lives of others. We also do not find it right in the religious sense to talk about sex/sexuality, because it is a sin to talk about sex/sexuality in our religion." (#1, 27 years old, Bachelor's degree, expecting his first child).

1.4. Expectant Fathers are not Willing to Receive Counseling on Sex/Sexuality

Approximately 50% of the expectant fathers who participated in this study stated that they did not want to receive counseling from healthcare professionals when they had problems regarding sex/sexuality; they believed that they were able to solve these problems by themselves, and they were ashamed of talking about sex and their sexual lives. The statement of an expectant father on the subject is as follows:

"Actually, I wanted to beat the doctor when he first asked me (questions about sexual life); I thought "how dare you ask me something like this?". I mean, I did not want to beat him up, but I just got angry since he questioned me about my privacy, but later I thought (on the subject) and I got used to it." (#29, 29 years old, Bachelor's degree, expecting his first child).

Theme 2. Sexual Life During Pregnancy

2.1. Pregnancy may Affect Sexual Life

All expectant fathers stated that their sexual life was negatively affected during pregnancy. They used to have sexual intercourse 3-4 times per week before pregnancy, and this frequency decreased, or their sexual life completely disappeared during pregnancy. Expectant fathers indicated that their sexual life was negatively affected because of reasons such as the fear of harming the baby, the belly growth, and the limitation of the mother's movements. The statements of two expectant fathers are as follows:

"When you know that your wife is pregnant, you still want to have sexual intercourse, but you have a fear of harming the baby inside her. I mean, if your normal routine is to do it every day before pregnancy, it decreases to once or twice a week during pregnancy; you become worried or afraid, the doctor does not say anything, but you become psychologically disturbed." (#8, 39 years old, Bachelor's degree, expecting his first child).

"There is no situation in which you can hang in any position you want, so as a result of our thinking of the baby every time, we wonder if something is happening to it or we touch it or I am pressing down on it, so such things as that can be negative." (#18, 30 years old, master's degree, expecting his first child).

2.2. Pregnancy may Strengthen the Marriage and Increase the Bond Between Spouses

In this study, 13 expectant fathers stated that pregnancy strengthened their marriage, and pregnancy enhanced the bonds between spouses. The statement of an expectant father on this subject is as follows:

"It seems like we have become attached to each other more. Because we're happy that we'll become a complete family" (#24, 30 years old, Primary school graduate, expecting his first child).

2.3. The Effect of the Changes of the Body Image on Pregnant Women and the Fear of an Extramarital Affair

Six expectant fathers who participated in this study reported that their spouses might be uncomfortable with their physical appearance because of the weight they had gained, and might not feel as attractive as they used to feel since their belly had grown. As a result, they might have a sense of not being sexually desirable. In addition to this, four expectant fathers expressed that their spouses had a fear of being cheated on during pregnancy. The statements of two expectant fathers on this subject are as follows respectively:

"For example, she is so afraid of her body being deformed; she says "I have stretch marks on my body, get me a stretch mark cream," her feeling of not being desirable increases." (#6, 36 years old, Master's degree, expecting his first child).

"My wife generally questions this issue; she asks me 'if there is a problem for me (about not having sexual intercourse]' because of the rumors she has heard from people around for years like 'men cheat on their wives most during pregnancy." (#18, 30 years old, master's degree, expecting his first child).

2.4. Sexual Intercourse may Become Just a Duty During Pregnancy

In the study, 4 expectant fathers stated that sex might become just a duty during pregnancy and their sexual intercourse took place without the desire of their spouses. Only 2 of the expectant fathers emphasized that the sexual desire of their wives had increased during this period. The statements of two expectant fathers on this subject were as follows:

"Sexual activity turns into something else after a certain point. I mean, like a duty, rather than (taking place) out of a desire" (#11, 37 years old, Bachelor's degree, expecting his second child).

"But after I heard that she was pregnant, I continued for a while for another month or two at request of my wife" (#15, 37 years old, Bachelor's degree, expecting his second child).

DISCUSSION

Sex is one of the main daily activities of individuals. Among the physiological needs, Abraham Maslow emphasized the importance of sex in his basic human need theory by ranking it on top.[6] In this study, the expectant fathers stated that they defined sex as an indispensable need that brings happiness, pleasure, and satisfaction to men. The study conducted by Rust et al.[19] emphasized that sexual activity was very important in marriage for men. Their findings are parallel to the findings of the present study. That result may arise from the fact that men view sex as an action aimed at ensuring their sexual satisfaction as well as the continuity of their lineage.

The fact that couples do not discuss their sexual life negatively affects their sexual relations. It also causes many conflicts among spouses.[20] Expectant fathers stated that they could not talk about their feelings regarding their sexual lives with their spouses. In the study conducted by Cakir Kocak[21], almost all of the expectant fathers (90%) stated that they could comfortably talk about subjects related to their sexual lives with their spouses during pregnancy. In a study conducted with pregnant women, they emphasized that they talked about sex with their husbands and got information from them.[8] Turkish men have difficulties in talking about sex with women, and still view this matter as a taboo topic.

In the present study, it appeared that expectant fathers are reluctant to make discussions regarding their sex lives. In addition, expectant fathers reported that sex is seen as a sin in their religion. As far as the literature is concerned, there are no studies reporting that the expectant fathers are not willing to talk about their sex lives. However, in a study conducted by Torun et al.[22] which aimed at investigating the beliefs about sexual myths and the factors affecting belief in these myths among Turkish men, while the majority of men responded to all of the questions, more than a quarter of men did not want to answer questions about relevant sexual experiences. The results of our study can be explained by the fact that sex and sexuality are seen as taboo topics in our country, just as in other developing countries.

Additionally, expectant fathers do not seem to be willing to receive counseling regarding sex. In the study conducted by Bilen Sadi and Aksu[16], 63.8% of expectant fathers were determined not to get information, which is in parallel with the results of our study. In the study conducted by Seturk Erenel et al.[9], 64.3% of pregnant women were found to not have received counseling on their sexual life during pregnancy from health professionals. The results of our study can be explained by the fact that sexuality and sexual life are still considered as a subject which must be kept secret in our society, as well as by the fear of men of being perceived as weak by others if they disclose such matters.

The sex life of expectant fathers is negatively affected during pregnancy due to reasons such as the fear of harming the baby, avoidance of risking the life of the baby, and the restriction of the mother's movements due to the growth of her belly. In the studies conducted by Radoš et al.[15] and Onah et al.[17], researchers concluded that the sexual desire, the frequency of sexual intercourse and the sexual satisfaction of expectant fathers decreased during pregnancy due to reasons such as fear of harming the baby and fear of miscarriage; while erection problems could also be frequent. Studies on pregnant women and their spouses emphasize that the fear of harming the fetus, stress, fatigue, and weakness are followed by a decrease in sexual desire and discomfort during sexual intercourse, which negatively affect the couple's sexual life during pregnancy.[3-5,7] These findings are in parallel with the findings of the present study. However, it was emphasized that overall sexual satisfaction and function were not problematic for couples during pregnancy based on the Golombok-Rust Inventory of Sexual Satisfaction scale in the another study by Dwarica et al.[23]. In other reviews in the literature, it is stated that sex is normal in pregnancy and there are very few proven contraindications and risks to intercourse in low-risk pregnancies.[24] In addition, it was emphasized that recommendations for or against restricting sexual activity should follow evidence-based guidelines.[25]

Pregnancy may increase the love between spouses and may strengthen the bond of marriage.[2] In some studies, it was determined that expectant fathers paid more attention and were closer to their wives, and also expressed love to them more during pregnancy.[26,27] In our study, expectant fathers stated that pregnancy increased the intimacy between them and their spouses. This result might have arisen from the peculiarities of the individual characteristics of the expectant fathers and the dynamics of their marriage. In addition, it can be explained by the fact that positive emotions related to the future new member of the family make the attachment between spouses stronger since the concept of family is given much importance and value in Turkish society.

The expectant fathers stated that their spouses were affected by the changes in their body image and accordingly afraid of the possibility of an extramarital affair by them. Similarly, Olsson et al.[28] found that the sexual life of pregnant women whose body image was distorted, who felt overweight and who believed that their husbands considered them ugly, were adversely affected. In the study conducted by Bilen Sadi and Aksu[16], 37.1% of expectant fathers stated that their wives were sexually attractive, even though they had gained weight. In the study carried out by Bello et al.[29] to determine Nigerian women's experiences and opinions about their postpartum sexual experiences, 26% of women reported that they accepted sexual intercourse in order to prevent their husbands' infidelity. In another study conducted in Nigeria, women were indicated to have sexual intercourse with their partners during pregnancy since they were afraid of their partners' infidelity.[30] As we have seen in studies conducted before, there are usually fears of unfaithfulness in pregnant women who live in Middle Eastern countries. When the population of Mersin is examined, it can be seen that there is a lot of migration from the Southeast region of Turkey. Apart from this, hormonal changes in estrogen and progesterone may also influence mood and body image in pregnant women, in addition to their increasing body weight. Therefore, women are expected to experience such fears caused by increasing body weight and changing body image during pregnancy.

In conclusion, sex is generally viewed by expectant fathers to be a duty, which is fulfilled mostly due to the sexual desire of the husband. Nevertheless, some studies support the fact that the sexual desire of pregnant women increases during pregnancy.[7,31] The result of the present study might have arisen from the fact that expectant fathers did not want to have sexual intercourse due to a fear of harming the fetus and/or the mother.

Study Limitations

Being a qualitative research, the results of this study are not representative and should be carefully interpreted. In addition, other limitations of this study are its small sample size and the fact that it was derived from a specific area of Turkey with certain cultural characteristics.

CONCLUSION

This study is the first qualitative study which investigates the sexual life of expectant fathers during pregnancy in Turkey, addressing possible problems which may emerge during this period. According to the content analysis, two main themes were developed as a result of this study. The first theme "*Feelings and thoughts on sexuality*", revealed that sex was very important for expectant fathers, but this was not communicated between the spouses, and expectant fathers did not want to talk about their sex lives. The other theme, "*Sexual life during pregnancy*", showed that pregnancy affected their sexual life, and it strengthened the marriage and the bonds between spouses. The themes also revealed that the wives of expectant fathers were disturbed by their changing body images and feared that their husbands might engage in extramarital relationships, and sexual intercourse might become only a dull duty during pregnancy. Therefore, these findings may guide physicians and nurses in planning counseling and training services which could be provided to expectant fathers since healthcare professionals play a critical role in helping people maintain a healthy sexual life.

In accordance with the results obtained from the present study, the researchers recommend forming an integrated service model in which expectant fathers are also included in the prenatal preparation classes which provide services for pregnant women in order to address the topics that expectant fathers are curious about and need to know about the during pregnancy. In addition, more research is needed, including both qualitative and quantitative studies, in order to look into this interesting aspect of sexuality and sexual activity more thoroughly and investigate possible intercultural differences.

MAIN POINTS

- These results give data on the feelings and thoughts regarding the sexual lives of expectant fathers during pregnancy.
- These results give data on the sexual lives of expectant fathers during pregnancy.
- The most striking result of this study is that all expectant fathers stated that their sexual life was negatively affected during pregnancy.
- According to these results, nurses should plan training and counseling which will cover both partners in the prenatal period.

ETHICS

Ethics Committee Approval: All procedures were approved by Mersin University Social Sciences Institutional Ethics Review Board (approval number: 2017/53) and Mersin University Health Research and Application Center (approval number: 41993462-774.001.0600000443843).

Informed Consent: In addition, all the participants signed informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A.C., D.Y.V., M.Y., Design: A.A.C., D.Y.V., M.Y., Supervision: D.Y.V., M.Y., Materials: A.A., M.Y., Data Collection and/or Processing: A.A.C., D.Y.V., M.Y., Analysis and/or Interpretation: A.A.C., D.Y.V., M.Y., Literature Search: A.A.C., Writing: A.A.C., Critical Review: A.A.C., D.Y.V., M.Y.

DISCLOSURES

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RESEARCH ARTICLE

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Investigation of Non-Painful Tactile Stimuli in Sleep: Amplitude and Frequency Analysis

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Abstract

BACKGROUND/AIMS: The aim of this study was to investigate evoked potentials elicited in the brain by non-painful tactile stimuli during sleep in amplitude-time and frequency-time domains.

MATERIALS AND METHODS: Ten volunteers attended this study (mean age: 22.30±1.49 years). Non-painful, single type tactile stimuli were applied to the index and middle fingers of the volunteers' right hand. During the night, the electroencephalography (EEG) of the subject was recorded via 40 channel EEG amplifier. The stages of the sleep were determined according to the standards of the American Academy of Sleep Medicine. Continuous wavelet transform was used for frequency analysis. The amplitude-time and the frequency-time findings relating to the periods of prior to sleep (PS), light sleep (LS), deep sleep, and REM were examined.

RESULTS: While P50, N100, P200, N300, P900 and N_late components were observed both during the PS and the LS periods, the P350 and N450 were observed only in the PS, and the P450 and N550 components were observed only during the all-night sleep periods.

CONCLUSION: In this study, it was also demonstrated by frequency-time analysis that there is a different information processing process during the PS and all-night sleep stages. In addition, with this study, we opened the way to show the dynamics of the non-painful somatosensory area associated with sleep stages.

Keywords: Amplitude, frequency, tactile awareness in sleep, wavelet transform, evoked frequency responses in sleep

INTRODUCTION

The examination of the brain's responses to external stimuli during sleep can be useful in investigating the structure and functions of sleep. Even further, the processing of external stimuli varies between sleep and wakefulness. Hence, sleep can be regarded as a different level of consciousness.[1-3]

Basically, a polysomnography (PSG) system is used to record sleep. PSG refers to the recording (and analysis) of many different physiological data at the same time during sleep. Some main recording components are required for the determination of sleep stages. These are electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG). In addition to these components, additional ones are used to monitor changes in respiratory and cardiac parameters, continuous blood pressure, snoring, body position etc. in order to determine sleep physiology and disorders. The sleep recorded with the PSG system is divided into stages with the standard sleep scoring methods.

While the guidelines of Rechtschaffen and Kales (R&K) had been used in the determination of sleep stages until 2007, the rules of the American Academy of Sleep Medicine are used today in determining sleep stages.[4] Sleep is not a steady state, rather it consists of constantly changing stages. One of these stages is the REM stage with rapid eye movements,

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and the other is NREM (without rapid eye movements). Typical NREM sleep consists of three sub-stages. These stages are stage 1 (N1), stage 2 (N2), and stage 3 (N3). In the literature, the N1 and N2 stages are accordingly named as light sleep (LS), while N3 is named as deep sleep (DS) or delta sleep.

The first stage seen in the transition from wakefulness to sleep is N1. In this stage, EEG signals are low amplitude and mixed frequency activity is seen, although the theta band (4-7 Hz) is more prominent. Slow eye movements are observed in EOG, and tonic muscle activity is observed in EMG. In the N2 stage, sleep spindles and K-complexes with a frequency of 11-16 Hz are seen. K-complexes are sharp waves consisting of a negative and a subsequent positive component. In the N3 stage, high amplitude (>75 μV), 0.5-2 Hz frequency delta activity is observed. During this stage, muscle tone decreases. REM shows signal characteristics very similar to N1. However, while rapid eye movements are seen in EOG, muscle tone decreases in EMG.[4]

There are a limited number of studies in the literature examining brain responses to non-painful tactile stimuli during sleep in healthy adults.[1,5,6] Frequency analysis was not found to have been used for evoked potentials in sleep studies. In the literature, frequency analyzes were generally applied in determining sleep stages.[7,8]

In this study, it was aimed to investigate brain responses to non-painful tactile stimuli in sleep healthy individuals with amplitude-time and frequency-time space.

MATERIALS AND METHODS

This study is a descriptive study for the examination of brain responses in the PS and all-night sleep stages in terms of amplitude-time and frequency-time space.

Subject

The study was conducted with 10 volunteers (5 females and 5 males; age range 22.30±1.49 years). None of the participants reported any psychiatric, neurologic, chronic illnesses or sleep disorders. In addition, their sleep behavior, coffee intake and or other sleep altering conditions were reported.

Scales

Following the introductory remarks of the study design and procedures, the participants filled in a number of reports and scales. These included the Edinburgh Handedness test, the STAI Form TX-1, SCL-90R tests, the sleep quality and daytime sleepiness Pittsburgh SQI and the Epworth Sleep scale.

The Sleep Laboratory

The volunteers went through a first night of sleep in an isolated room. The room was designed with a Faraday cage to minimize electric and electromagnetic noise and spikes. Furthermore, acoustic isolation provided a conveniently quiet room. The room was dimly lit. An interactive audio system enabled communication when necessary. The entire session was video recorded with real time stamps.

Recording System

The PSG recording was managed by the NuAmps 40 channel (EEG, EOG, EMG) system together with the Embedded Microcontroller Stimulation Unit,[9] pneumatic stimulation unit (Somatosensory Stimulus Generator 4-D Neuroimaging) and recording PC unit.

During the EEG recording, the participants wore an appropriate size Quick Cap (Neuromedical Supplies). The cap enabled a long-term comfortable whole-head recording and conductance was assured with the electro gel (Electro-Gel, Electro-Cap International, Inc. US). EEG referencing was managed by interlinked ear lobe electrodes [(A1+A2)/2].

The eye movements of the participants were monitored by electrodes placed at the outer canthus of the right eye and left supraorbital areas. EMG activity was monitored by electrodes placed over the supra and inferior chin areas. The overall electrode impedance was targeted to be kept lower than 5 KOhm and continuous EEG recording sampling was maintained at 1 KHz sampling frequency.

Experimental Design and Stimuli

The non-painful tactile stimulation was enabled by a pneumatic stimulation unit (4-D Neuroimaging Somatosensory Stimulus Generator).

Tactile stimulations were administered using a modified finger clip mechanism over the index and mid fingers of the right hand during the entire sleep period. The modified finger clip mechanism incorporated a moving membrane with a contact area radius of 8-9 mm. This membrane was positioned to apply a soft pressure over the finger tips. The pneumatic stimulation unit administered a certain amount of air upon being triggered via an in-house MATLAB stimulation system. This pressurized dry air puff action would move the membrane, thus resulting in a soft touch sensation on the participants' finger tips.

The current study was composed of a single type of tactile pressure stimulation. The experimental design had blocks of 60 stimulations that would repeat about 10 times throughout the night. Each block duration was 7 to 8 minutes and the interval between the blocks were about 40 minutes. The inter stimulus interval was around 3 to 3.5 seconds and the order of the stimulations was randomized.

Ethics Statement

This study was approved by the Institutional Ethics Evaluation Board [Dokuz Eylül University Non-Invasive Research Ethical Committee (approval number: 2011/16-16)]. Consent of individuals was obtained before starting the recordings. The participants were given detailed information about the research and the methods to be applied to them in the study. Individuals who agreed to participate in the study filled in the informed volunteer information and consent form and signed that they participated in the study voluntarily.

Statistical Analysis

EEG evaluation was carried out post session after recording. The stages of sleep records were determined according to the AASM scoring system. The 30-second-long recordings were examined one-by-one and the N1, N2, N3 and REM stages were evaluated.

The stimuli and consequent responses (EEG traces) were evaluated separately for all sleep stages.

The epochs were arranged as 1000 ms pre-stimulus and 2000 ms post-stimulus sweeps. Out of these sweeps, the corresponding EOG channel was monitored and any amplitude exceeding ±100 μV was eliminated. Furthermore, baseline correction and 0.5-30 Hz band pass filter (digital

band filter with 12 dB/oct and zero phase shift, Neuroscan 4.5) were applied. Following these procedures, average files were formed for each sleep phase and each participant. Out of the 40 channel EEG recordings, for the sake of simplicity (which is already among the region of interest for non-painful tactile stimulations), only central (Cz) electrode potentials were reported in this manuscript.

The amplitude measurements were taken as 0-2000 ms maximum responses (μV). Following this, continuous wavelet transform was applied to the epochs to provide visual scalogram for frequency-time space. This study consisted of NREM sleep with two subcategories of N1 and N2 assessed as LS while N3 was assessed as DS (LS and DS respectively). The rapid eye movements stage results were also assessed as REM.

RESULTS

In the current study, PS records and all-night sleep (LS, DS, REM stages) sessions were evaluated for all of the participants. None of the participants reported or showed any signs of anxiety, chronic, psychiatric or neurological disorder, nor any sleep disorder. All of the volunteers were right-handed (handedness score: 91.00±9.94).

The non-painful tactile stimulations were successfully obtained from all of the above-mentioned stages. The waveforms resulted in average deflections of certain time windows. Thus, these were labelled as P50, P50, N100, P200, N300, P900 and N_late. To clarify, the P and N denote positive and negative deflections, whereas the numbers refer to the time window of the waveform (latency after stimulation in ms). Out of these waveforms, P350 and N450 were observed only in wakefulness, while P450 and N550 were sleep waveforms.

Prior to Sleep

In the period before sleep, the latency of the response components against painless tactile stimuli (applied to the right-hand index and middle fingers) were examined. Here, the P50 component appeared 94 to 148 ms after the stimulus. Among the prominent peaks, N100 fell into 132-204 ms, P200 appeared from 210 to 290 ms, N300 response was observed between 274 to 360 ms, P350 was at 316 to 424 ms, N450 from 398 to 550 ms, P900 ranged from 646 to 926 and N_late was observed from 1164 to 1352 ms (Table 1).

The brain responses to non-painful tactile stimulation during the wakeful period resulted in the following amplitudes of wave deflections.

Table 1. Prior to sleep wakefulness period for non-painful tactile responses

	Latency (ms) Mean ± SD	Amplitude (μV) Mean ± SD
P50	125.00±19.58	1.74±1.43
N100	178.40±22.09	-1.92±2.58
P200	237.20±25.69	2.74±2.48
N300	309.20±23.16	-0.56±2.22
P350	356.00±31.82	1.37±1.97
N450	465.40±53.22	-3.22±2.24
P900	829.00±81.09	2.02±1.16
N_late	1,256.40±58.20	-1.52±0.94

The latency periods (ms) and peak to peak maximal amplitudes (μV) are presented in columns. Each measurement is accompanied by the standard deviation values. SD: standard deviation.

P50 ranged from 0.04 to 5.16 μV, N100 from 0.41 to -7.04 μV, P200 from 0.44 to 8.08 μV, N300 from -4.86 to -3.22 μV, P350 varied from -0.98 to 5.68 μV, N550 waveform was observed between -0.75 to -8.70 μV, P900 as 0.25 to 4.06 μV and finally N_late from -0.40 to -3.13 μV. These values are shown in table form with their standard deviation as well (Table 1).

The prior to sleep (PS) stimulus waveforms are shown as both amplitude-time and frequency time domains in Figure 1. The time values are represented in the range of 0.5-1.5 s and their frequency range from 0 to 5 Hz.

Light Sleep

During the whole night recording, N1 and N2 stage EEG segments (denoted as light sleep, LS) were evaluated for right-hand index and mid-finger tactile responses. This led to sleep tactile waveforms with positive and negative deflections. The latencies for P50 waveforms were between 64-170 ms, N100 from 90 to 242 ms, P200 ranged from 166 to 290 ms, N300 varied from 258 to 388 ms, P450 appeared from 440 to 560 ms, N550 were observed from 484 to 774 ms, P900 from 668 to 900 ms and N_late from 954 to 1,292 ms. The brain responses to non-painful tactile stimulation during the LS period resulted in the following amplitudes of wave deflections. P50 ranged from -0.73 to 1.93 μV, N100 from 1.14 to -2.17 μV, P200 from -0.11 to 3.02 μV, N300 from -0.96 to -9.31 μV, P450 varied from 0.17 to 6.74 μV, N550 waveform was observed between 1.57 and -1.03 μV, P900 was -0.16 to 4.18 μV and finally N_late was from -0.74 to -3.51 μV. These values are given in table form with their standard deviation in Table 2.

The wavelet transformed waveforms are shown in Figure 2. Here, the frequency and amplitude domains in time provide us with the specific frequency shifting patterns of sleep induced brain activities.

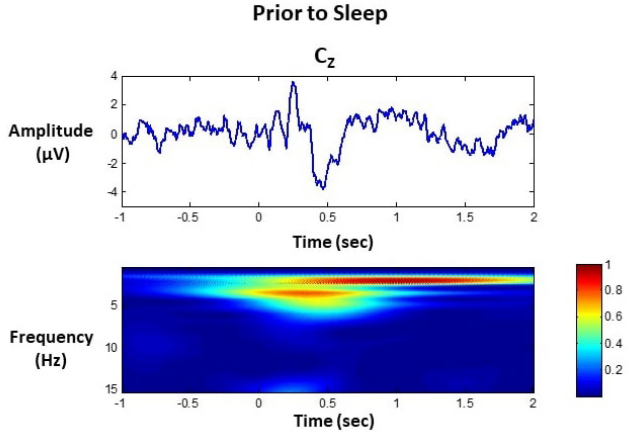

Figure 1. The average prior to sleep wakefulness responses from 10 volunteers to non-painful tactile stimulations (applied to right-index and mid-finger tips) are presented from central electrode (Cz). The upper panel represents the electrophysiological waveform. Here, the vertical axis denotes amplitude in μV and the horizontal axis shows time values (in seconds from -1 to 2 seconds). The "0" in the time axis represents the time of tactile stimulation. The lower panel shows the scalogram in frequency and amplitude domains. The scalogram provides the frequency-time in the horizontal axis while the vertical axis is denoted by frequency time (in Hz). The amplitude information is provided by a color bar next to the figure.

Furthermore, the responses are given as frequency-amplitude-time space. Accordingly, the first 500 milliseconds following the tactile stimulations were prominent in 0 to 5 Hz whereas the late responses from 500 milliseconds onwards resulted in a diminished activity.

Deep Sleep

In the course of the whole night sleep, N3 stage EEG segments (denoted as deep sleep, DS) were evaluated for right-hand index and mid-finger tactile responses. This led to typical sleep tactile waveforms with positive and negative deflections. The latencies for P50 waveforms were between 86-122 ms, N100 from 132 to 246 ms, P200 ranged from 180 to 306 ms, N300 varied from 310 to 386 ms, P450 appeared from 446 to 574 ms, N550 were observed from 490 to 658 ms, P900 from 658 to 808 and N_late from 964 to 1,136 ms.

Table 2. The light sleep (N1 and N2 non-REM stages) period non-painful tactile responses (recorded from Cz)

	Latency (ms) Mean ± SD	Amplitude (μV) Mean ± SD
P50	114.20±25.84	0.90±0.73
N100	162.00±40.47	-0.41±0.91
P200	222.00±33.74	1.40±1.03
N300	333.00±34.17	-3.69±2.51
P450	485.40±34.65	1.67±1.96
N550	589.60±90.26	0.00±0.75
P900	741.40±68.10	1.41±1.27
N_late	1,100.20±123.41	-1.66±0.89

The latency periods (ms) and peak to peak maximal amplitudes (μV) are presented in columns. Each measurement is accompanied by the standard deviation values. SD: standard deviation.

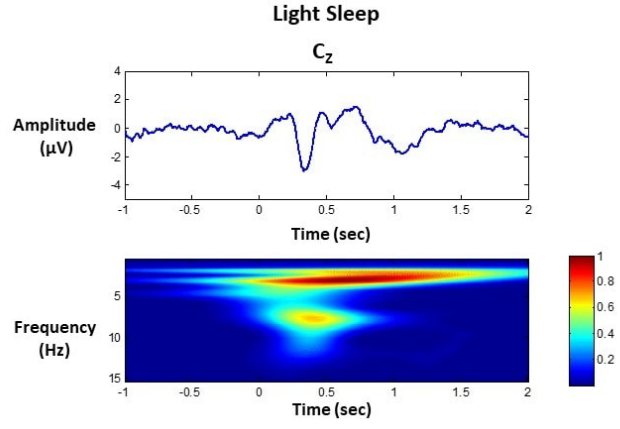

Figure 2. The average light sleep stage responses from 10 volunteers to non-painful tactile stimulations (applied to right-index and mid-finger tips) are presented from central electrode (Cz). The upper panel represents the electrophysiological waveform. Here, the vertical axis denotes amplitude in μV and the horizontal axis shows time values (in seconds from -1 to 2 seconds). The "0" in time axis represents the time of tactile stimulation. The lower panel shows the scalogram in frequency and amplitude domains. The scalogram provides the frequency-time in horizontal axis while the vertical axis is denoted by frequency time (in Hz). The amplitude information is provided by the color bar next to the figure.

The brain responses to non-painful tactile stimulation during the DS period resulted in the following amplitudes of wave deflections. P50 ranged from -0.05 to 2.39 μV, N100 from 1.73 to -2.87 μV, P200 from -0.65 to 3.51 μV, N300 from -1.26 to -11.22 μV, P450 varied from -0.28 to 8.53 μV, N550 waveform was observed between 4.60 and -1.00 μV, P900 was from -0.23 to 6.21 μV and finally N_late from -1.30 to -6.04 μV. These values are given in table form with their standard deviations (Table 3).

The brain responses are presented in a scalogram of frequency-amplitude space. This allows us to evaluate the changes specific to this stage. The activity as a response to tactile stimulations are also present in the DS stages (Figure 3).

Table 3. The deep sleep (N3 non-REM stage) period non-painful tactile responses (recorded from Cz)

	Latency (ms) Mean ± SD	Amplitude (μV) Mean ± SD
P50	105.60±12.10	1.06±0.80
N100	159.80±33.22	-0.21±1.25
P200	215.60±35.19	1.37±1.34
N300	345.00±22.16	-4.85±3.26
P450	511.20±40.12	2.41±2.60
N550	577.50±59.40	0.53±1.80
P900	719.00±40.61	2.51±2.19
N_late	1,028.40±52.96	-3.43±1.88

The latency periods (ms) and peak to peak maximal amplitudes (μV) are presented in columns. Each measurement is accompanied by the standard deviation values. SD: standard deviation.

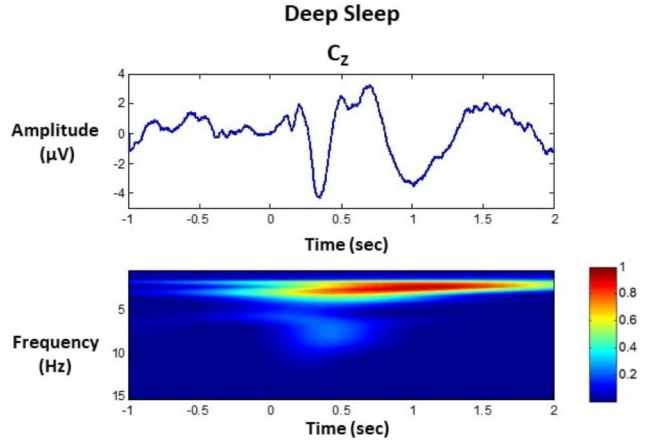

Figure 3. The average deep sleep stage responses from 10 volunteers to non-painful tactile stimulations (applied to right-index and mid-finger tips) are presented from central electrode (Cz). The upper panel represents the electrophysiological waveform. Here, the vertical axis denotes amplitude in μV and horizontal axis shows time values (in seconds from -1 to 2 seconds). The "0" in time axis represents the time of tactile stimulation. The lower panel shows the scalogram in frequency and amplitude domains. The scalogram provides the frequency-time in horizontal axis while the vertical axis is denoted by frequency time (in Hz). The amplitude information is provided by the color bar next to the figure.

REM

Via the throughout-the-night recording, the REM segments were evaluated for right-hand index and mid-finger tactile responses. This led to a number of waveforms in positive and negative deflections. The latencies for P50 waveforms were between 70-150 ms, N100 from 122 to 172 ms, P200 ranged from 202 to 272 ms, N300 varied from 296 to 372 ms, P450 appeared from 396 to 494 ms, N550 were observed from 452 to 668, P900 from 668 to 900 ms and N_late from 820 to 1,098 ms. The brain responses to non-painful tactile stimulation during the REM period resulted in the following amplitudes of wave deflections. P50 ranged from -0.07 to 1.69 μV, N100 from 0.43 to -1.75 μV, P200 from 0.22 to 2.20 μV, N300 from -0.58 to -3.23 μV, P450 varied from 0.37 to 1.84 μV, N550 waveform was observed between 0.40 to -2.16 μV, P900 as 0.10 to 1.55 μV and finally N_late from -0.09 to -1.18 μV. The values are shown in table form with their standard deviations (Table 4).

Observing the related scalogram in the frequency-amplitude space, the peak Z dimension (bright red colors, see attached color bar) values are confined to the early stage of the post-stimulus time domain (Figure 4).

The REM specific activity of the brain as a response function to external stimulations are represented in Figure 4. Here, also the frequency-amplitude scalogram is provided.

DISCUSSION

Our project and its results are the first study examining external tactile stimulation assessed in the frequency specific domain in healthy individuals. A review of studies even with a broader scope reveals a limited number of studies within the somatosensory domain.[1,5,6]

Wakefulness recordings are reported as 8-13 Hz sinusoidal or 0.5-2 Hz conjugated eye movements in the literature. The sleep stage N1 presents 4-7 Hz oscillations, N2 as 11-16 Hz, whereas N3 shows 0.5 to 2 Hz oscillations.[4]

Our study incorporated the PS period rather than daytime wakefulness. This also enabled the extension of this recording into regular PSG. Accordingly, the evoked frequency response revealed higher activity of 0-5 Hz in 0.5 s to 1 s, and lower activity of 0-5 Hz within -1 to 2 s time range. As N1 and N2 sleep stages were regarded as LS, the cortical responses to tactile stimulations resulted in high activity in the 0-5 Hz frequency band in the 0.5 s to 1 s window, and a low activity in the 5-10 Hz band at 500 ms.

The DS (N3) results revealed lower activity in the lower frequency band during the early phase (0.5 s) and 0-5 Hz band high activity at the 1 s time mark. During the REM recordings, the 0 to 0.5 s period revealed high activity in the 5 to 15 Hz band.

The current study reveals external tactile processing in the form of frequency responses as well as sleep stage related oscillatory shifts.

The sleep literature contains a number of studies on amplitude and latency differences in the auditory modality used to assess the brain processing during sleep.[2,3,10] Similar to the current study, the brain responsiveness continued throughout the sleep stages including DS. Thus, the auditory and tactile processes can be effectively used as cognitive tools for sleep research. The current study expands the scope to PS, and also into frequency-amplitude space.

We propose that the current method proposed in this manuscript may pave the way to become a standard domain for enlightening the cortical processing during sleep as well as providing insight to automated sleep assessment research.

Sleep studies have long benefitted from electrophysiological signals, namely PSG. However, this heavily relies on sleep experts to evaluate hours long data. This data analysis is more on the appearance of waveforms in certain time frames etc. Thus, in a number of cases, inter-rater reliability or reproducibility can be questionable.

The time stamps of complex stimulations are also not available in these classical systems. Hence a new approach is necessary to provide further understanding of this domain. The tactile signals are of an interesting

Table 4. The REM sleep stage period non-painful tactile responses (recorded from Cz)

	Latency (ms) Mean ± SD	Amplitude (μV) Mean ± SD
P50	107.20±25.69	0.56±0.65
N100	154.00±16.68	-0.69±0.69
P200	231.80±20.14	1.14±0.64
N300	329.00±20.25	-1.94±0.83
P450	439.20±34.18	1.16±0.57
N550	558.00±75.05	-0.66±0.72
P900	769.80±59.94	0.50±0.43
N_late	959.60±95.53	-0.69±0.31

The latency periods (ms) and peak to peak maximal amplitudes (μV) are presented in columns. Each measurement is accompanied by the standard deviation values. SD: standard deviation.

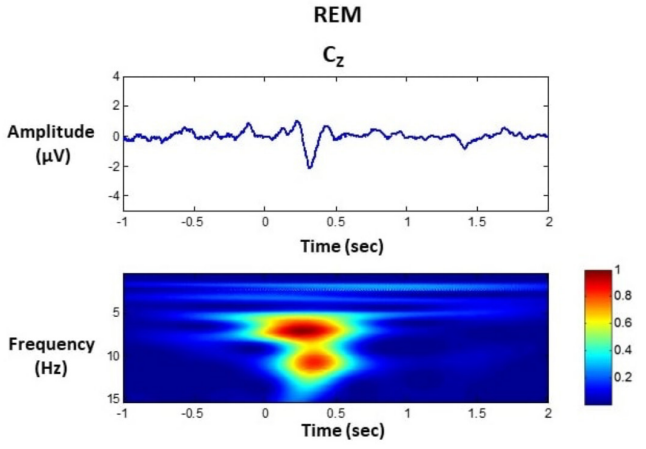

Figure 4. The average REM (rapid eye movements) sleep stage responses from 10 volunteers to non-painful tactile stimulations (applied to right-index and mid-finger tips) are presented from central electrode (Cz). The upper panel represents the electrophysiological waveform. Here, the vertical axis denotes amplitude in μV, and the horizontal axis shows time values (in seconds from -1 to 2 seconds). The "0" in time axis represents the time of tactile stimulation. The lower panel shows the scalogram in frequency and amplitude domains. The scalogram provides the frequency-time in horizontal axis while the vertical axis is denoted by frequency time (in Hz). The amplitude information is provided by the color bar next to the figure.

nature as they not only have an influx of information from the outside world, but also they have been widely used in BCI methods.[11]

The brain reveals to us not only the spontaneous activity of the background and even state changes (i.e. the shifts of sleep stages), but also the responsiveness of the brain to the external world. This relies on both sensory processing as well as cognitive capacity. The so-called sleep-tactile-relationship is a fresh step to address these issues.

The bottom-up to top-down processing of the brain paves the way for us to reveal brain connectivity and dynamic processing. The further tools that might be used may include the coherence, frequency domain approach as well as entropy.

Sleep is not a state of an unconscious brain. We have (similar to a number of other studies) hereby shown that even in DS, the brain is "open" to outside stimulation. Therefore, the brain continuously responds to the outside world even in a limited or altered capacity. It is no wonder that tactile stimulation is also a common practice to wake someone up in addition to the auditory stimulation. Here, we have paved the way to show the dynamics of the non-painful somatosensory domain in relationship to sleep stages.

An interesting phenomenon should also be addressed at this stage. The brain while being monitored with external stimulations, in fact, could alter its state due to the stimulus itself. Therefore, we may liken this to Schrodinger's cat, where observing a scientific phenomenon may itself be including alterations to the original state. However, the brain is the ultimate organ which serves as an external stimulation processor throughout our life cycle. No wonder one is regarded as dead only with the death of the brain.[12] The brain computer interface era is fast approaching so any objective data set with the same set of parameters across a healthy population by itself is a useful measure.

CONCLUSION

The responsiveness of the brain during sleep therefore can be regarded as a useful tool to shed light on the human brain. Finally, the current speculative approach to the brain for longer hibernation states etc. require objective screening of the brain in various states of brain functioning. Accordingly, our method could provide insight to somatosensory processing, disorders of the tactile nature, the brain in altered states etc.

MAIN POINTS

- Sleep studies constitute an increasingly important area in the field of human health.
- The current study is a pioneering one into how tactile stimuli are processed at every stage of sleep by frequency and amplitude analysis and also in comparison to immediately before sleep.
- This study may interest a wide audience of health-related scientists, sleep based neuroscientists, clinical and basic scientists, etc.
- In addition, the responses to tactile stimuli have been examined from an engineering point of view.
- Accordingly, we believe this manuscript will open a window to further sleep research methodology.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Ethics Evaluation Board [Dokuz Eylül University Non-Invasive Research Ethical Committee (approval number: 2011/16-16)].

Informed Consent: Consent of individuals was obtained before starting the recordings.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.I., M.O., A.O., Design: G.I., M.O., A.O., Supervision: M.O., A.O., Fundings: M.O., A.O., Materials: G.I., M.O., Data Collection and/or Processing: G.I., Analysis and/or Interpretation: G.I., Literature Search: G.I., M.O., A.O., Writing: G.I., M.O., A.O., Critical Review: G.I., M.O., A.O.

DISCLOSURES

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

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RESEARCH ARTICLE

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The Effect of the COVID-19 Pandemic on Elbow Trauma in the Pediatric Population

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Abstract

BACKGROUND/AIMS: The coronavirus disease-2019 (COVID-19) pandemic has had significant effects on children's daily activities. Changes in the patterns of pediatric trauma injuries were inevitable. Therefore, we aimed to identify the effects of lockdown during the COVID-19 pandemic on the etiology and epidemiology of pediatric elbow injuries.

MATERIALS AND METHODS: A retrospective analysis was performed on pediatric patients admitted to the emergency room with elbow trauma during the first 3 months of the pandemic (11th, March, 2020 to 11th, June, 2020) and for the same periods in 2019 and 2018. Age, sex, etiology and type of injury (distal part of humerus, proximal radius and ulna, nursemaid's elbow and soft tissue injuries) were analyzed and compared between the periods.

RESULTS: A total of 152 patients, 61 in 2018, 56 in 2019 and 35 in 2020 were included. There were 42.7% and 37.5% decreases in the number of patients during the pandemic compared to 2018 and 2019, respectively. A younger age group was more commonly affected during the pandemic (p=0.01). The most common type of injury was supracondylar humerus fracture followed by soft tissue injury in both periods, before and during the pandemic. During the pandemic, the rates of injuries at home, in the playground and by vehicles (car, bicycle, scooter) increased while outside injury decreased significantly (50.4%, p<0.05).

CONCLUSION: The COVID-19 pandemic caused a decline in the frequency of pediatric elbow injuries but the increase in injuries at home and vehicle accidents have shown the necessity for health-care to be prepared for these specific conditions.

Keywords: Pediatric, elbow injury, COVID-19, fracture, pandemic

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was reported first in China on the 31st of December, 2019 and it became a global pandemic situation.[1] The high-speed spread of SARS-CoV-2 resulted in a declaration of pandemic by the World Health Organization on the 11th of March, 2020.[2] On the same day, the Ministry of Health declared the first case in Turkey. Since then, the government started to impose restrictions which caused inevitable changes in daily activities. Measures such as the closure of schools, restaurants, cinemas, and shopping malls where the virus can easily spread, restriction on going out for those under the age of 20, and shift working systems were put in place. Some changes in the epidemiology of pediatric trauma patients presenting to emergency rooms were expected because of the precautions to limit the spread of this virus.[3-11]

Elbow fractures are the one of most common fractures seen in children. It is important to determine which part of the elbow is involved and the fracture type as each of them has a unique diagnosis and treatment option. Supracondylar fractures, lateral condyle fractures, radial neck

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fractures, and medial condyle fractures are the most common types of elbow fractures.[12,13]

Restrictions and precautions have affected the daily activities in all age groups of the population. However, there are still limited resources regarding the impact of the COVID-19 pandemic on the trauma mechanisms of the pediatric population. We aimed to report our tertiary care center experiences including the effects of the COVID-19 pandemic on the rates, etiology and types of pediatric elbow injuries, and to compare the current results with the same time periods of the previous two years. Our hypothesis was that the COVID-19 pandemic would decrease the frequency of elbow traumas and change the etiology and types of elbow injuries.

MATERIALS AND METHODS

This study was approved by the Ministry of Health of Turkey on the 26th of June, 2020 and the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2020/20-32, date: 31.08.2020).

This study was a retrospective analysis and it included those patients who were consulted in the department of orthopedics and traumatology from the pediatric emergency room with elbow injuries during the period starting the 11th of March until the 11th of June, 2020 and the same periods for 2018 and 2019. Those patients who were over 18 years of age, re-admitted with the same fractures or had multi- or poly-trauma injuries were excluded. Totally, 117 patients for 2018 and 2019 and 35 patients for 2020 were included. The patients' age, gender, time of admission to hospital, side of fractures, types and the etiology of their injuries were analyzed.

Radiographic classifications were carried out by three orthopedic surgeons; E.Ş., O.G., C.T. (2 consultants and 1 senior residence surgeons) via open discussion. Final decisions were reached based on a majority vote. The etiology of the injury was recorded as home, outside, playground or vehicle accidents (car, bicycle, scooter). The types of injury were divided into supracondylar, medial and lateral condyles of the humerus, proximal radius and ulna, nursemaid's elbow or soft tissue injuries of the elbow.

Statistical Analysis

The distributions of data were checked with the Kolmogorov-Smirnov normality test. Continuous variables were represented by mean and standard deviation. The differences were compared using the Independent samples t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical data are given as number and percentage (%). Chi-square test with Bonferroni adjusted post-hoc tests was used in the analysis. All analyses were carried out on the SPSS for Windows (version 22.0; IBM Corp, Armonk, NY, USA). A p-value below 0.05 was accepted as statistically significant.

RESULTS

A total of 152 patients, 61 in 2018, 56 in 2019 and 35 in 2020 were admitted to the hospital. There was a 42.7% decrease in the number of patients during the pandemic period compared with 2018 and 37.5% compared with 2019. Demographic features are shown in Table 1. There was no statistical difference between genders (p=0.33). The mean age was higher in the pre-pandemic period with a statistically significant difference (p=0.01) as there was a 23.5% increase in the percentage of children who were <6 years age during the pandemic period (Figure 1). In both periods, most of the patients were admitted to the hospital on the same day as their injury (87.2% for the pre-pandemic period and 80% for the pandemic period). Right side injuries were more common in both periods.

Table 1. Demographic data for the pre-pandemic and pandemic periods

Characteristics	Pre-pandemic 2018 and 2019, n (%)	Pandemic 2020, n (%)	p
Total number	117 (100)	35 (100)	-
Gender			
Male	65 (55.6)	16 (45.7)	0.33*
Female	52 (44.4)	19 (54.3)	
Age			
Minimum-maximum (mean ± SD)	2-18 (8.1±4.1)	1-16 (6.1±4.1)	0.01**
<6	36 (30.8)	19 (54.3)	
6-11	53 (45.3)	12 (34.3)	
≥12	28 (23.9)	4 (11.4)	
Days to admission hospital, minimum-maximum (median)	0-3 (0)	0-3 (0)	-
0	102 (87.2)	28 (80)	0.75***
1	11 (9.4)	6 (17.1)	0.64***
2	3 (2.6)	0 (0)	0.80***
3	1 (0.9)	1 (2.9)	0.85***
Side of injury			
Right	68 (58.1)	21 (60)	0.5*
Left	49 (41.9)	14 (40)	
Total	117 (100)	35 (100)	

SD: standard deviation, n: number, *chi-square test, **Mann-Whitney U test, ***chi-square post-hoc test.

A comparison of the frequencies of the types of injury is given in Table 2. The most common type of injury for the pre-pandemic period was supracondylar humerus fracture (49.6%), followed by soft tissue injury

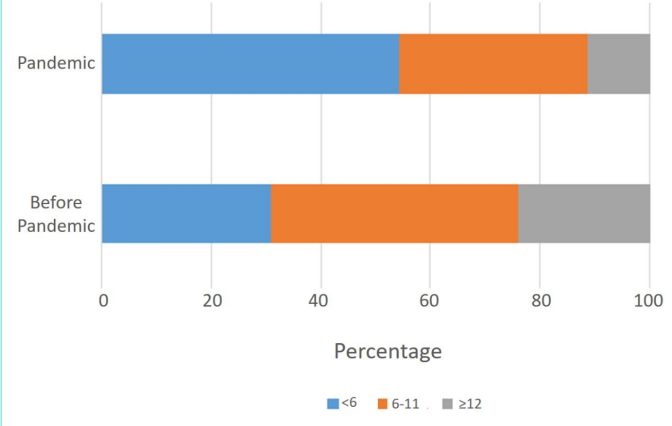

Figure 1. Comparison the percentage of age groups between the pre-pandemic and the pandemic periods.

Table 2. Comparison of injury type rates between the pre-pandemic and pandemic periods

Type of injury	Pre-pandemic 2018 and 2019, n (%)	Pandemic 2020, n (%)
Supracondylar humerus	58 (49.6)	17 (48.6)
Lateral condyle	6 (5.1)	1 (2.9)
Medial condyle	1 (0.9)	1 (2.9)
Proximal radius	4 (3.4)	0 (0)
Proximal ulna	10 (8.5)	3 (8.6)
Nursemaid's elbow	4 (3.4)	1 (2.9)
Soft tissue injury	34 (29.1)	12 (34.3)
Total	117 (100)	35 (100)

Table 3. Comparison of differences in injury place rates between the pre-pandemic and pandemic periods

Place of injury	Pre-pandemic 2018 and 2019, n (%)	Pandemic 2020, n (%)	p*
Home	27 (23.1)	16 (45.7)	0.08
Outside	69 (59)	3 (8.6)	<0.05
Playground	14 (12)	6 (17.1)	0.88
Vehicle accident (car, bicycle, scooter)	7 (6)	10 (28.6)	0.02
Total	117 (100)	35 (100)	

*chi-square post-hoc test.

(29.1%) and proximal ulna fractures (8.5%). During the pandemic period, the ranking of the type of injury was the same. The percentage of supracondylar humerus fractures in both groups were approximately half of the total population. No proximal radius fractures in the pandemic period were seen. The percentage of soft tissue injuries increased during the pandemic period by 5.2%.

There were some differences between the surroundings where the injury occurred (Table 3). 59% of elbow injuries in the pre-pandemic period occurred outside, while 45.7% of injuries during the pandemic occurred at home. During the pandemic, the proportion of injuries at home, in the playground and due to vehicles increased by 22.6%, 5.1% and 22.6%, respectively. Only the vehicle accident subgroup resulted in a statistically significant difference (p=0.02). During the pandemic, all of the vehicle accidents were caused by bicycles while five out of seven vehicle accidents were caused by bicycles in the pre-pandemic group. However, the proportion of outside injuries was the only subgroup that decreased significantly during the pandemic (50.4%, p<0.05).

DISCUSSION

Based on our study, the COVID-19 pandemic decreased the frequency of elbow injuries in the pediatric population. Additionally, the mean of age decreased during the pandemic period. The type of injury did not change between the periods. However, the common etiology of injury shifted from outdoor accidents to home accidents.

The lockdown period included the closure of schools, playgrounds, sport centers, and full lockdowns for over 65 and under 20-year olds. These precautions inevitably affected the frequency of pediatric fractures including elbow injuries.[3-11] We have detected approximately a 40% decrease in the pediatric population with the elbow injuries during the pandemic period compared to the same periods of the previous two years.

Although there was no statistically significant difference in gender between the two periods, the number of girls was more than boys during the pandemic period. Some studies have reported that there was no difference in gender distribution but fractures were more common in boys than in girls.[5,10,14] These different data could be a result of including fractures and soft tissue injuries together in this study.

Injuries related to the playground, school activities and home accidents are common in the childhood population, while in adolescents, the common causes of injuries are vehicle accidents caused by falling from bicycles, scooters etc., and outside activities such as sport injuries.[15-20] We observed a decrease in the outside injuries of approximately 50% while we noticed an increase in home injuries of more than 20% during the pandemic compared to the same periods of the previous two years. We thought that these changes were the results of the lockdowns and restrictions on public areas. The mean age of the patients decreased during the pandemic period, while vehicle accidents increased by more than 20%. We expected to see just the opposite result. However, the closure of playgrounds and social distancing precautions probably led parents to encourage the use of individual vehicles (scooters, bicycles etc.) for their children. Interestingly, there was a slight increase in the percentage of injuries which occurred in playgrounds. The reason for this could be due to an increase in the percentage of children who tried to spend their limited free time outside of the lockdown in playgrounds instead of just being outside in public areas such as the street.

In both periods, more than 80% of patients applied to hospital on the day that their injuries happened. While some centers had similar results, delays in other disciplines have also been observed.[6,11,21,22]

50-70% of all elbow injuries in children are composed of supracondylar humerus fractures. These types of fractures are seen mostly in falls onto an out-stretched upper extremity. In this study, nearly half of the cases were caused by supracondylar humerus fractures which is due to the fact that these mostly happen with low energy falls.[23] Carkci et al.[7] reported an increase in pediatric supracondylar humerus fractures during the pandemic as a result of the effects of quarantine on children's psychology and difficulties in keeping them at home. Turgut et al.[10] had similar results in that they found that distal humerus fractures were the second most common anatomical location for pediatric fractures. Elbow fractures have some potential to cause serious problems in skeletally immature populations.[12] In the literature, recommendations on decreasing home injuries were seen.[24,25] We think it is necessary for health authorities to make guidelines on this topic.

Our center has the one of the biggest orthopedics and traumatology clinics located in the third most populous city in Turkey, and thus, its capacity and facilities have to be enough to provide healthcare to a wide range of the population. This situation makes the results of our study acceptable to evaluate the impact of COVID-19 more generally.

Study Limitations

This study has obvious limitations due to its retrospective nature. First of all, we have reported on only a single institution's experiences and these may not reflect the epidemiology of the whole population. We did not include all pediatric trauma patients admitted to emergency room, but only those who were examined in orthopedic clinics regarding

their elbow injuries. Therefore, it is difficult to analyze the rate of elbow trauma in all kinds of trauma admitted. We did not evaluate the treatment preferences and results and we excluded any re-admissions with the same fractures in order to avoid any biases which may have resulted from complications of treatments. Parents might prefer to take their children to less crowded or private clinics in order to avoid infection from COVID-19. This condition might have decreased the admittance of trauma patients to our center. Therefore, our results may not represent the correct rates of elbow injury patterns. Multicenter studies could shed light on the distribution of elbow injuries and the effects of COVID-19 on elbow injuries.

CONCLUSION

The COVID-19 pandemic caused an approximate 40% decrease in the frequency of pediatric elbow injuries, and it led to a decrease in the mean age of the patients. During the pandemic, the number of girls was more than boys. Supracondylar humerus fractures were still the most common type of elbow injury. Injuries at home and vehicle accidents increased by 22.6% while outside injuries decreased by 50.6% during the pandemic period. This study shows the necessity for parents to take care of their children while at home and when on vehicles, such as scooters and bicycles, in order to prevent injuries.

MAIN POINTS

- An approximately 40% decrease in the pediatric population with the elbow injuries was detected between the pre-pandemic and pandemic periods.
- We observed a decrease in outside injuries of approximately 50% while we observed an increase in home injuries of more than 20% during the pandemic period in comparison to the same periods of the previous two years.
- The mean age of patients decreased during the pandemic period.

ETHICS

Ethics Committee Approval: This study was approved by the Ministry of Health of Turkey on the 26th of June, 2020 and the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2020/20-32, date: 31.08.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Ş., O.G., Design: E.Ş., Supervision: O.G., Materials: C.T., Data Collection and/or Processing: C.T., Analysis and/or Interpretation: E.Ş., Literature Search: E.Ş., O.G., C.T., Writing: E.Ş., O.G.

DISCLOSURES

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

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RESEARCH ARTICLE

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Chimerism Analysis of Children with Allogeneic Stem-Cell transplantation and Its Effect on Survival

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Abstract

BACKGROUND/AIMS: Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is an important and usually the only curative clinical tool for treating pediatric patients with many hereditary and acquired diseases. Although complete donor stem cell engraftment is the desired result of Allo-HSCT, patients do not always have a definite engraftment and end up with mixed chimerism. Many factors both related to patient and transplantation can affect chimerism levels. Additionally, mixed chimerism levels may affect the event free survival (EFS) differently in distinct diseases. The major goals of this study were to determine the first 100-day donor chimerism ratios and to search for a relationship between donor chimerism success (CS) (for malignant diseases, hematopoietic donor chimerism >95%; for non-malignant diseases, >70%) and EFS for pediatric patients.

MATERIALS AND METHODS: We collected data from 95 pediatric patients who underwent Allo-HSCT between March, 2005 and April, 2010 at Ege University Hospital with at least one chimerism result obtained within the first 100 days.

RESULTS: After checking for all other factors, CS in the first 100 days increases the chance of post-transplant EFS by -3.04 (-4.00 to -2.08) [hazard ratio (HR): 0.05 ($p<0.001$)]. Neutrophil engraftment was the other factor which was positively correlated with EFS (HR p-value: 0.05)

CONCLUSION: There is a positive correlation between CS in the first 100 days and EFS for both malignant and non-malignant diseases.

Keywords: Children, chimerism, stem-cell-transplantation

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the only curative treatment for many congenital and acquired, malignant and non-malignant diseases of the childhood period.[1,2] Donor stem cell engraftment is a critical step in the success of Allo-HSCT.[3] However, engraftment does not always result in a definite status and we may end up with mixed chimerism. Mixed chimerism is a state where both the recipient and donor hematopoietic stem cells coexist in the host's bone marrow.[4] Although malignancies require a full donor match (>95%), mixed chimerism may cure primary immunodeficiency and hemoglobinopathy.[5,6] Therefore, chimerism success (CS) for malignant diseases requires >95% donor cells, while for non-malignant diseases, a donor cell ratio of over 70% can be accepted as success. Many factors affect survival but the chimerism status of the first 100 days is a useful parameter to predict survival.[7] Understanding the factors and elements associated with CS in the first 100 days will help to improve overall survival (OS) in HSCT.[8] Serial analysis of the patient's chimerism levels at fixed time points and on suspicion of relapse or graft failure may be used to track engraftment levels, disease control, and relapse risk.[9]

With this study, we aimed to understand the factors affecting CS and event free survival (EFS) after Allo-HSCT in a mixed group of pediatric patients.

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MATERIALS AND METHODS

We retrospectively reviewed pediatric patients who had undergone allogeneic HSCT transplantation at Ege University and had at least one chimerism result obtained within the first 100 days. The Ege University Ethics Committee approved this study which was executed according to the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (approval number: 07-5.1-14, date: 08.08.2007). Chimerism statuses were assayed from bone marrow for the first month and peripheral blood for the second and third months. We defined CS as >95% and >70% for malignant diseases and non-malignant diseases, respectively. We investigated associations between CS with patient demographics, indications for HSCT, donor/graft, and post-transplantation factors. After DNA extraction was performed from samples, data about chimerism were collected using polymerase chain reaction (PCR) amplification of short tandem repeats of 15 polymorphic loci and one amelogenin with the AmpFlSTR® Identifiler® PCR Amplification Kit.

Statistical Analysis

For these collected nominal variables, univariate survival analysis was performed according to the Kaplan-Meier method and two-tailed log-rank analysis was used to detect statistically significant differences.[10] Parameters with p-values of <0.1 were included in the multivariate survival analysis. The Cox proportional hazards model was used for both univariate and multivariate analysis for continuous parameters. Probit regression analysis was used to investigate the effective causes of the success of chimerism. As a result of the evaluation of all independent parameters in this study, statistically insignificant parameters were removed and the Probit model was repeated.[11] Analyses were performed using Stata/SE 14.0.

RESULTS

In this retrospective study, we analyzed 95 pediatric patients who had undergone Allo-HSCT between March, 2005 and April, 2010 and had at least one chimerism result obtained within the first 100 days. The median age was 102 months and 58 (61.0%) were male. Leukemia (28%), thalassemia major (24%), and diseases associated with bone marrow failure (25%) were the most common reasons for undergoing HSCT. Most of the donors were matched sibling donors (Table 1). In 33 cases (35%), transplantation was from women to men, and the stem cell source was predominantly peripheral blood (58%). In three patients (3.2%) with severe combined immune deficiency, no conditioning regimen was used. A myeloablative conditioning regimen was used in 68.4% of patients, and non-myeloablative regimens were used in 28.4%.

Table 1. Transplantation characteristics

Char.	Groups		Patient number (n)	%	n	Range
Donor and HLA match (*)	MSD		75	79		
	MRD		9	10		
	MMRD		5	5		
	MUD		6	6		
Donor/recipient sex	M	M	25	26		
	F	F	19	20		
	M	F	17	18		
	F	M	33	35		
Stem cell source	Peripheral blood		55	58		
	Bone marrow		30	42		
	Cord blood		1	1		
	Bone marrow + cord blood		8	8		
Conditioning regimen	None		3	3		
	Myeloablative		65	68		
	Non-myeloablative		27	28		
CD34 (+) cell count (x10^6/kg)						
Median					5	0.2-44.4
GvHD prophylaxis	CSA		30	32		
	CSA + MTX		57	60		
	CSA + MMF		1	1		
	No prophylaxis		7	7		
WC engraftment						
(ANS ≥500/mm^3)			88	93		
(A)GvHD	Grade 0-1		72	76		
	Grade 2-4		23	24		
Disease	Relapsed		21	22		
	No relapsed		74	78		

MSD: matched sibling donor, MRD: matched related donor, MMRD: mismatched related donor, MUD: matched unrelated donor, M: male, F: female, GvHD: graft versus host disease, CSA: cyclosporine, MTX: methotrexate, MMF: mycophenolate mofetil, WC: white blood cell, (A)GvHD: (acute) graft versus host disease.

Table 2. Relation between patient and HSCT characteristics and event-free survival	
Patient or SCT characteristics	**p-value**
Sex	
Male/female	0.86
Age	0.16
Primary disease	
Malignant/non-malignant	0.24
Donor and HLA match	
MSD/MRD/MMRD/MUD	**0.01**
Host and donor sex differences	0.06
Stem cell source	
Peripheral blood, bone marrow, cord blood, bone marrow and cord blood	0.94
Conditioning regimen	
Myeloablative/non-myeloablative-no conditioning	0.32
CD34 (+) cell count (median, x10^6/kg)	
≥5/<5	0.05
Neutrophil engraftment	
Existing/absent	**<0.001**
(A)GvHD	
Existing/absent	0.27
VOD	
Existing/absent	0.32
First 100 days chimerism success	
Existing/absent	**<0.001**

HSCT: hematopoietic stem cell transplantation, SCT: stem cell transplantation, HLA: human leukocyte antigen, MSD: matched sibling donor, MRD: matched related donor, MMRD: mismatched related donor, MUD: matched unrelated donor, (A)GvHD: (acute) graft versus host disease, VOD: veno occlusive disease.

The median CD34+ cell count was 5x10^6 cells/kg (minimum: 0.27x10^6/kg, maximum: 44.4x10^6/kg). For graft versus host disease (GvHD) prophylaxis, 31.6% of patients received cyclosporine (CSA) only. In 56.8% of patients, CSA was combined with methotrexate, and in one patient, CSA was combined with mycophenolate mofetil.

In 92.6% of patients, neutrophil engraftment was observed between the 9th-36th (median 17th) days of HSCT. 24.2% of patients were diagnosed as having grade 2-4 acute GvHD. Veno-occlusive disease (VOD) was detected in eight patients (8.4%). 30.5% of patients either had a relapse of their primary disease or died of HSCT complications. 8.4% of patients died after SCT without relapse. In 22.1% of patients, primary disease relapse was detected, seven of whom died of disease relapse, the latest being at the 18th month of SCT. With a mean of 22 months of follow-up, the OS was 84.0% and even EFS was 69.5%.

We excluded four patients from the further analysis. Three of them were excluded from the analysis because they could not complete the first 100 days after SCT and one patient was re-transplanted within the first 100 days. Of these 91 patients, 77 (84.6%) had CS within the first 100 days. The CS was 84.4% and 84.7% in patients with malignant and non-malignant diseases, respectively.

We evaluated factors which affect EFS and our univariate analysis revealed that CS within the first 100 days, human leukocyte antigen (HLA) matched donors, the amount of CD34+ cells (over 5x10^6), and neutrophil engraftment were associated with EFS (Table 2). The patients' age, sex, primary disease type of the conditioning regimen, stem cell source, and the existence of GvHD or VOD were found to be unrelated to EFS. Parameters with p-values <0.1 were evaluated using multivariate analysis (Table 3). In multivariate survival analysis, we found that CS within the first 100 days, neutrophil engraftment, and female to female SCT were found to be related to EFS.

Discussion

Allo-HSCT is the only curative treatment method in many congenital or acquired childhood diseases.[12,13] Most of these diseases are acute leukemia and congenital diseases such as congenital bone marrow deficiencies (Fanconi anemia), hemoglobin synthesis defects (thalassemia major), congenital immunodeficiency, and some metabolic diseases (osteopetrosis), which are common in Turkey where consanguineous marriage is still widespread.[1] The fact that the primary diseases of the patients included in this study were extremely heterogeneous, the primary diseases were either malignant or non-malignant, and the patients who received myeloablative or non-myeloablative treatment were in the same pool made the evaluation difficult.

In this study, due to the shorter follow-up period compared with similar studies, instead of evaluating increasing, decreasing, and stable mixed chimerism,[13] CS within the first 100 days was evaluated as per Holtan et al.[14]. In the present study, 77 (84.6%) out of 91 patients achieved CS within the first 100 days, which is slightly higher than the findings of Ünal İnce et al.[15] regarding T. Major patients transplanted between 1999-2007 in Ankara, Turkey. Their rate was 84.4% in malignant diseases and 84.7% in non-malignant diseases. Although this rate varies according to the type of primary disease (malignant, non-malignant) and the type of conditioning regimen used (myeloablative, non-myeloablative), it was found to be 64% in the study of Holtan et al.[14].

Similar to the literature,[16,17] in univariate analysis, HLA-matched donor selection had a positive effect on EFS. However, multivariate analysis

Table 3. Multivariate analysis of parameters related with event free survival				
Independent variables	**RR**	**95% CI**	**HR**	**HR p-value**
First 100 days chimerism success	**-3.0432**	**(-4.0041 to -2.0824)**	**0.05**	**<0.001**
Existing neutrophil engraftment	**-0.8010**	**(-1.5876 to -0.0143)**	**0.45**	**0.05**
Female donor to female recipient	-2.1620	(-4.5000 to 0.1761)	0.12	0.07
HLA matched donor	-0.41	(-1.2684 to 0.4442)	0.66	0.28
CD34+ cell count over ≥5x10^6/kg	-0.12	(-1.1710 to 0.9216)	0.88	0.82

RR: risk ratio, CI: confidence interval, HR: hazard ratio.

showed no statistically meaningful effect. Again, in multivariate analysis, no difference was found when the donor's HLA-matched sibling was compared with other donor types. We think that no statistically significant results were obtained in the multivariate analysis due to the low number of transplants from unrelated donors in our patient group and the lack of long-term follow-up of these patients. It should be noted that in the study published by Holtan et al.[14] in 2010, donor type and HLA match were also found to have no positive effect on EFS. Contrary to the literature, in our study, CD34+ cell counts above the median value had no statistically significant effect on survival.[18]

Unlike the literature, in our study, the gender relationship between the donor and recipient was found to be associated with EFS.[19] Randolph et al.[20] showed that male recipients of female transplants had the lowest risk for relapse and the greatest odds for GVHD, however in our study, it was observed that female-to-female transplants had a positive effect on survival compared with the other groups. Regardless of all other parameters, the realization of neutrophil engraftment in the recipient positively affected EFS.

It was observed that the most important factor which affected EFS was CS within the first 100 days. The risk of recurrence and death decreased with CS within the first 100 days [hazard ratio: 0.05 ($p<0.001$)]. In previous studies on hematologic malignancies, 95% and above donor chimerism was shown to have a positive effect on EFS.[21] Our study suggests that donor chimerism of 70% or higher within the first 100 days may also have a positive effect on survival in non-malignant diseases.

Study Limitations

The low number of patients and the shortness of the follow-up period were the major limitations of this study. With more patients, longer follow-up and more chimerism results, we would be able to understand more about the relationship between chimerism and disease relapse in malignancy, and graft loss in non-malignant diseases. Although a significant amount of time has passed since the time of our study, the effects of chimerism on EFS have still not been clarified in the literature.[22]

CONCLUSION

The success of chimerism was found satisfactory in this heterogeneous patient group and CS within the first 100 days was the most important predictor of EFS.

MAIN POINTS

- In a heterogeneous group of pediatric Allo-HSCT patients, Chimerism Success within the first 100 days was the most important predictor of EFS.

ETHICS

Ethics Committee Approval: The Ege University Ethics Committee approved this study which was executed according to the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (approval number: 07-5.1-14, date: 08.08.2007).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.T., Design: H.T., S.A., D.C.T., S.K., Supervision: H.T., S.A., S.K., Materials: H.T., Data Collection and/or Processing: H.T., S.A., D.C.T., Analysis and/or Interpretation: H.T., S.A., Literature Search: H.T., Writing: H.T., S.A., D.C.T., Critical Review: S.A., S.K.

DISCLOSURES

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

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RESEARCH ARTICLE

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The Accuracy of Body Mass Index Estimated from Self-Reported Height and Weight in Turkish Adults

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Abstract

BACKGROUND/AIMS: This study aimed to identify the level of agreement between self-reported and objectively measured data among healthy Turkish adults in order to assess the validity of self-reported data.

MATERIALS AND METHODS: Self-reported data along with independent measurements were obtained from 958 men and 502 women, aged between 18-53 years. The subjects were classified according to their body mass index (BMI) scores and margins of error in self-reported anthropometric data were calculated. The misclassification status according to BMI deriving from self-reported data was determined. Intraclass correlation coefficients were calculated at 95% confidence interval. Independent sample t-test and One-Way ANOVA were used for comparisons. Bland-Altman graph, specificity and sensitivity, Cohen's kappa and receiver operating characteristic curve inspections were carried out.

RESULTS: The results indicate that both men and women underestimated their weight and overestimated their height. The margin of error in estimating height for the men was found to be significantly larger than for women. In contrast, women tended to underestimate their weight more than men. The subjects' self-reported and measured anthropometric data were significantly different ($p<0.01$) in both sexes. Specificity scores were found to be high but sensitivity scores were low.

CONCLUSION: These results indicate that the subjects' margins of error were large and that BMI assessment through self-reported data can lead to erroneous estimates when used to assess obesity in Turkish adults and BMI should not be relied on unless the scores are obtained by objective anthropometric measurements.

Keywords: Validity, sensitivity, specificity, obesity

INTRODUCTION

Body mass index [(BMI); kg/m^2)], calculated as mass (kg) divided by the height squared (m^2), is a well-known and widely used measure to assess body composition and obesity prevalence.[1] The anthropometrical variables used to calculate BMI are commonly self-reported data in epidemiological studies.[2] Although it has limited predictive power on personal body composition assessment[3] and the accuracy of such data is widely questioned, it is still the most commonly used measure to assess obesity in broad groups all over the world, not only because it only requires basic anthropometric data, namely, height and weight[4] but also because the assessment is non-invasive, inexpensive and easy-to-use.[5] Self-reported data is a useful tool to calculate BMI in large groups, especially when it is impractical to take independent measurements.[6]

Many studies use self-reported data, either raw or calculated, as a data collection method as it is easier, faster, and more economical than direct measurements.[7] Social scientists, in general, use self-report to collect data because of the high cost of collecting data by measurement.[8] It is widely recognized that self-reports of body weight

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and height are often inaccurate[1,9] and studies suggest that self-reported height and weight tend to be inaccurate and biased when compared to objectively measured data.[10] Such inaccuracies may prevent researchers from determining the obesity levels of a population.[7,11] Although some previous studies suggested that BMI scores obtained using self-reported height and weight were highly correlated with objectively measured BMI scores,[12,13] overweight, and elderly people along with women tend to underestimate their weight while overestimating their height.[5,7]

Obesity has been known to be a major public health issue since the late 1980s[14] and in today's world, monitoring the obesity level of a large group is important to identify obesity-related health problems, premature death rates,[11,15] and occupational health status.[16] Some studies[5,17] have attempted to suggest a correction factor for self-reported data in BMI classification, but no successful solution has been provided to date because the mechanism underlying the inaccuracy in self-reported BMI is unknown.[4] Other ways to correct self-reported BMI, such as using the Stunkard Figure Rating Scale, were found to be impractical because they relied on the body image perceptions of individuals.[5]

In today's world, governments look for solutions to prevent obesity at the individual level and to slow down or reduce obesity levels in the population.[4,18] High BMI levels are related to certain types of cancer,[19,20] ischemic heart disease,[21] cardiorespiratory fitness,[22] and low quality of life levels.[23] Obesity is known to contribute to cancers at a rate of about 6% in the U.S. population[24] and it is also associated with cardiorespiratory fitness.[25]

Many countries have set some public policies and public health goals to prevent obesity at the individual level and to slow down obesity rates at the population level[4] and BMI is widely used in determining these public health policies.[3]

Numerous studies have been conducted in several countries and regions, including the U.S.A., France, South America, Great Britain, Scandinavian countries, Australia, New Zealand, and Eastern countries to assess the association between self-reported and measured anthropometric data but only limited research on Turkish adults has been carried out. This study aimed to assess the association between self-reported and measured BMI categorizations in Turkish adults and to test the validity of self-reported anthropometric data.

MATERIALS AND METHODS

Participants

The participants who volunteered to take part in this study were aged 18 and over. This cross-sectional study was carried out between September, 2018 and June, 2019. Data were collected in the Çorum province of Turkey. The participants were comprised of university students, urban and rural people, attendees and spectators of public meetings such as academic year opening ceremonies, art exhibitions and other events such as sporting games. Over 2,000 people were invited to take part and, of these, a total of 1,460 individuals agreed to take part in this study.

Data Collection

The subjects were informed about the aim of this study and their written consent was obtained. The subjects were asked to fill out a questionnaire including their anthropometric data. A Seca (model 703) professional weighing-scale was used to measure weight to 1/100 of a kilogram and a Seca (model 220) stadiometer was used to measure height to 1/10 of a centimetre accuracy. Measurement errors were minimized by applying standard operating procedures strictly and calibrating the measurement devices regularly.

Ethics Approval

The study protocol was approved by the Non-Interventional Researches Ethics Committee of Hitit University (approval number: 2018-07).

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation and quartiles of the anthropometric data are also given. The normality of the data was tested and found to be normally distributed. Intraclass correlation coefficients (ICCs) were calculated at 95% confidence interval (CI). The Independent sample t-test was used to analyse differences between dichotomous groups; One-Way ANOVA was used for analysis between three or more groups. Bland-Altman graphs were created to inspect the level of agreement between the self-reported and measured anthropometric data. Specificity and sensitivity scores were calculated to assess the levels of conformity of the self-reported BMI values. Cohen's Kappa was also calculated to assess the strength of agreement between the self-reported and objectively measured BMI categorization. SPSS (IBM Corp. 2013, Release 22.0.0.0, 64-bit edition; Licensed to Hitit University) was used for statistical analyses.

RESULTS

A total of 1,460 participants, aged 18 to 52 (31.91±8.18 years) participated in this study and the number of men (n=958) was nearly twice the number of women (n=502). The subjects' measured and self-reported height, weight, and BMI values were included in the data analyses. The subjects' gender, marital status, level of education, level of income, and smoking status were also used for statistical calculations.

Margins of error were calculated as the difference between the self-reported and measured values (self-reported minus measured). Those scores below zero reflect underestimation and those scores over zero reflect overestimation.

ICCs were 0.944 (95% CI: 0.939-0.960) for height, 0.971 (95% CI: 0.968-0.974) for weight and 0.878 (95% CI: 0.866-0.890) for BMI between the self-reported and measured values for the variables. All measurements for the variables revealed very high concordance but BMI had the lowest ICC value.

A summary of the statistics regarding the anthropometric measurements by gender is shown in Table 1. Men over-reported their heights by 1.99±1.86 cm while women over-reported by 2.82±1.71 cm. The self-reported weight margin of error for men was -0.77±2.33 kg and it was -1.08±2.39 for women. Both men and women underestimated their weight but overestimated their height. Women were prone to underestimate their weight and overestimate their height more than men. Analysis of BMI values yielded similar results and the difference between the reported and measured BMI data for men was -0.78±0.98 kg/m^2 and -1.18±1.07 kg/m^2 for women. The differences between the reported and measured weight, height, and BMI data for men and women were statistically examined using the independent sample t-test and all found to be significant ($p<0.001$ and $p<0.05$). The subjects in the overweight/obese category significantly overestimated their heights and underestimated their weights and BMI scores when compared to normal category subjects ($p<0.001$).

Table 1. Summary of statistics by gender

	Male (n=958)				Female (n=502)				p†
	Q_1	Q_2	Q_3	Mean ± SD	Q_1	Q_2	Q_3	Mean ± SD	
Age (years)	25	32	37	31.83±8.27	25	31	38	32.05±8.03	0.630
Height (cm)									
Measured (H_M)	169.7	174.5	181.8	175.63±8.43	161.4	166.4	169.8	165.52±5.57	0.000*
Self-reported (H_R)	172	177	183	177.62±8.00	165	169	172	168.33±5.48	0.000*
Difference ($H_D = H_M - H_R$)	0.6	1.9	3.4	1.99±1.86	1.6	3.0	4.0	2.82±1.71	0.000*
(%) difference ($100 \cdot H_D/H_M$)	0.36	1.09	1.96	1.15±1.08	0.96	1.84	2.41	1.71±1.05	0.000*
Weight (kg)									
Measured (W_M)	66.8	72.8	79.7	73.28±10.38	59.9	66.4	70.6	65.70±9.78	0.000*
Self-reported (W_R)	67	72	78	72.51±9.56	59	65	69	64.62±8.68	0.000*
Difference ($W_D = W_M - W_R$)	-2.10	-0.80	0.60	-0.77±2.33	-2.33	-1.10	0.30	-1.08±2.39	0.021**
(%) difference ($100 \cdot W_D/W_M$)	-2.86	-1.06	0.83	-0.86±3.24	-3.50	-1.71	0.40	-1.39±3.45	0.000*
BMI (kg/m²)									
Measured ($B_M = W_M/H_M^2$)	21.98	23.99	24.90	23.74±2.88	22.58	24.00	25.29	23.95±3.20	0.223
Self-reported ($B_R = W_R/H_R^2$)	21.63	23.16	24.30	22.96±2.45	21.69	22.79	23.84	22.77±2.62	0.165
Difference ($B_D = B_M - B_R$)	-1.35	-0.75	-0.14	-0.78±0.98	-1.81	-1.13	-0.48	-1.18±1.07	0.000*
(%) difference ($100 \cdot W_D/W_M$)	-5.44	-3.10	-0.63	-3.06±3.95	-7.37	-4.86	-2.08	-4.65±4.08	0.000*

†Independent samples t-test, *p<0.001, **p<0.05, SD: standard deviation.

The mean differences between the measured and self-reported height, weight, and BMI values were not significantly different in any of the categories as shown in Table 2. Gender was found to cause statistically significant differences in reporting bias. Women overestimated their height (p<0.001) and underestimated their weight (p<0.05) and consequently the BMI scores of women were much lower when compared to men (p<0.001). The level of education, marital status, monthly income, and smoking status resulted in no significant differences between the measured and self-reported data (p>0.05). All groups tended to overestimate heights and underestimate weights. As a result of this general tendency, the self-reported BMI in each category was lower than the measured BMI.

The differences between the self-reported and measured data by age groups are summarized in Table 3. ANOVA results (Table 4) yielded no significant differences between the age categories (p>0.05).

The Bland-Altman plot of weight estimation errors demonstrated a slightly skewed distribution. The subjects tended to underestimate their weight by up to 9.4 kg and overestimate by up to 6.1 kg. The plot of height estimation error revealed that most of the subjects overestimated their heights, by up to 8.5 cm, but underestimated by only up to 2.9 cm.

The Bland-Altman plot of BMI errors revealed that the self-reported and measured data did not have a good level of agreement. A very large portion of the subjects' BMI data was underestimated by up to 4.77 kg/m² but overestimated by only 1.81 kg/m². The plots support that the belief that the subjects have a strong tendency to overestimate their height and underestimate their weight (Figure 1).

The map of estimation errors presented a clear picture of the bias of the subjects. Most of the errors are pooled in the lower-right quadrant which represents both an overestimation of height and an underestimation of weight. Subjects who overestimated their weight and underestimated

Table 2. Differences by categories

Categories		Height difference (mean ± SD)	p†	Weight difference (mean ± SD)	p†	BMI difference (mean ± SD)	p†
Gender	Male	1.99±1.86	0.001*	-0.77±2.33	0.015**	-0.78±0.98	0.001*
	Female	2.82±1.71		-1.08±2.39		-1.18±1.07	
Level of education	K12	2.28±1.84	0.893	-0.84±2.28	0.491	-0.91±1.01	0.780
	University	2.27±1.87		-0.93±2.45		-0.93±1.05	
Marital status	Single	2.28±1.86	0.800	-0.93±2.34	0.198	-0.94±1.02	0.369
	Married	2.26±1.84		-0.77±2.36		-0.89±1.04	
Monthly income	Below average	2.31±1.83	0.283	-0.9±2.41	0.533	-0.94±1.05	0.311
	Average or above	2.20±1.89		-0.82±2.23		-0.88±0.99	
Smoking status	Non-smoker	2.29±1.90	0.835	-1.05±2.26	0.084	-0.99±1.01	0.055
	Smoker	2.27±1.82		-0.76±2.41		-0.88±1.04	

†Independent samples t-test, *p<0.001, **p<0.05, BMI: body mass index, SD: standard deviation.

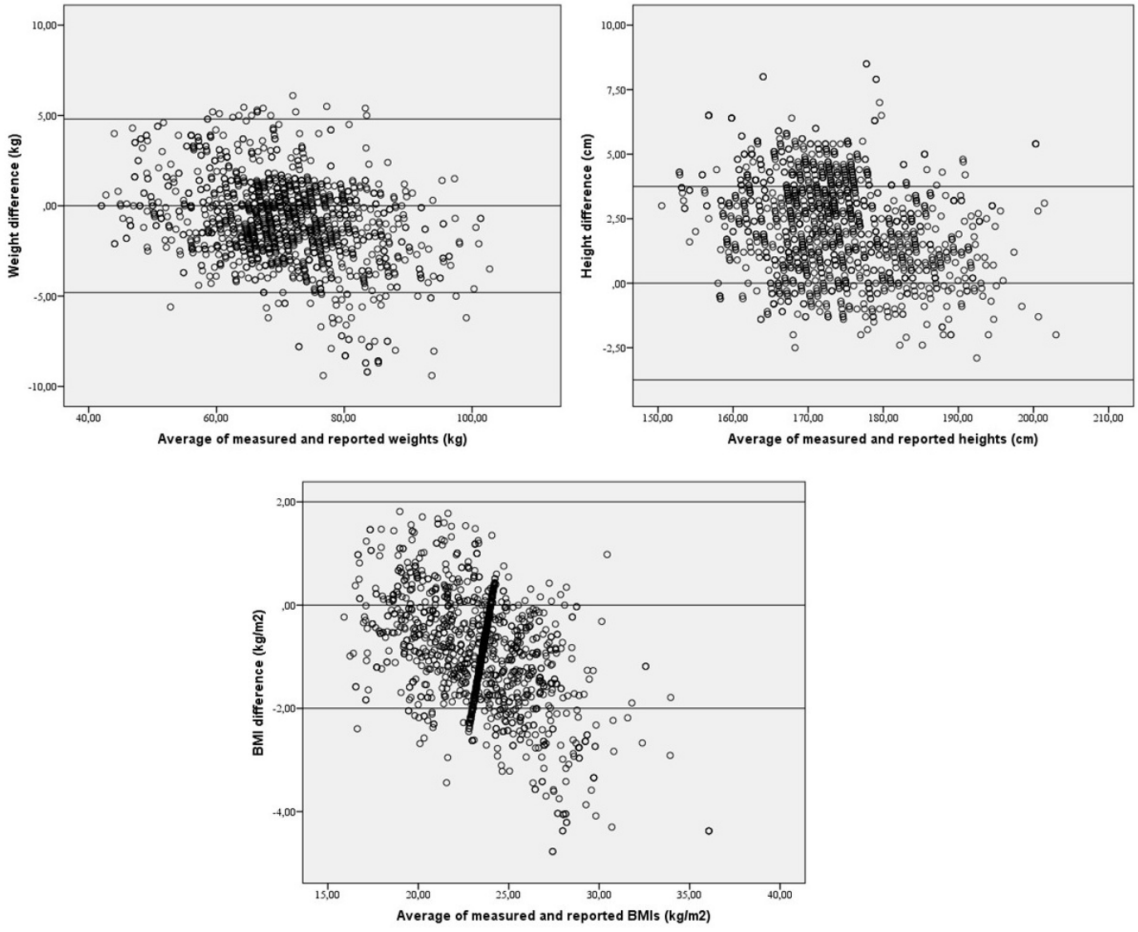

Figure 1. Bland-Altman plots of weight, height, and BMI errors.
BMI: body mass index.

their height are in the upper-left quadrant and the number of these subjects was fairly small (Figure 2).

Figure 3 (graph on top) shows that all of the obese class II subjects underestimated their BMI scores and the rate of underestimation of BMI scores decreased as the level of obesity decreased. Over 90% of the obese class I subjects and more than half of the overweight subjects underestimated their BMI scores. The subjects in the normal and underweight categories did a fairly good estimation and both categories accurately estimated their BMI scores at about 80%. Only about 10% of all subjects overestimated their BMI scores but no overestimation was observed in the overweight, obese class I, or obese class II subjects. As stated previously, agreement on BMI estimation was set at ±1.40 kg/m^2 between the self-reported and measured data.

The rates of estimation consistency between the self-reported and measured BMI scores are given in Figure 3 (graph on bottom). Less than 10% of the subjects correctly reported their BMI scores. All of the obese subjects (both class I and II) and more than 95% of the overweight subjects underestimated their BMI scores. About 45% of the underweight and 20% of the normal subjects overestimated their BMIs. Except for a limited number of overweight subjects, no subjects above the normal range overestimated their BMI scores.

Table 3. Differences between self-reported and measured anthropometric data by age groups

Age groups (years)	n	Height difference (cm)		Weight difference (kg)		BMI difference (kg/m^2)	
		Mean	SD	Mean	SD	Mean	SD
18-29	597	2.23	1.90	-0.88	2.35	-0.90	1.02
30-39	609	2.30	1.83	-0.83	2.26	-0.91	1.00
40-49	224	2.31	1.83	-1.06	2.54	-1.02	1.10
50 and over	30	2.31	1.68	-0.24	2.68	-0.71	1.15

BMI: body mass index, SD: standard deviation.

Table 4. ANOVA statistics by age categories

		Sum of squares	df	Mean square	F	p
Height difference (cm)	Between groups	1.765	3	0.588	0.17	0.921
	Within groups	5004.24	1456	3.437		
	Total	5006.01	1459	-		
Weight difference (kg)	Between groups	20.443	3	6.814	1.23	0.302
	Within groups	8045.66	1456	5.526		
	Total	8066.11	1459	-		
BMI difference (kg/m^2)	Between groups	3.636	3	1.212	1.15	0.328
	Within groups	1540.15	1456	1.058		
	Total	1543.79	1459	-		

BMI: body mass index.

The receiver operating characteristic (ROC) graphs indicate the accuracy of the self-reported BMI for men and women. The area under the curve for men was 0.71 (95% CI: 0.667-0.751) and 0.76 (95% CI: 0.718-0.803) for women (Figure 4). The statistics for ROC curves of the BMI accuracy levels are summarized in Table 5.

The specificity of the self-report was almost perfect (≥99.7%) but its sensitivity was only 69.5% for men, about 59.4% for women, and 65.9% overall (Table 6). Cohen's kappa was also calculated to assess the strength between the self-reported and measured BMI categories and Kappa was found to be 0.678 (SE: 0.020, p<0.001).

DISCUSSION

Reporting weight and height accurately is an essential part of obesity assessment via self-reported anthropometric data.[1] Although the strength of association between self-reported and measured BMI categories show substantial agreement in this study,[26] the accuracy of self-reported data has always been questioned and many authors have raised concerns,[27-30] while some others have championed its effectiveness.[14,31] There are many factors which affect the accuracy of self-reported data and it has been previously reported that the accuracy of self-reported anthropometric data is affected by certain variables.[32] The main variable which affects the accuracy of self-reported BMI is reported to be gender.[33] In a study conducted to assess the accuracy of self-reported anthropometric data in Scottish adults,[11] both sexes tended to misestimate their height and weight. In their study, Bolton-Smith et al.[11] found that self-reported anthropometric data differed from the measured data by gender. Men tended to overestimate their height but underestimate their weight in a similar way to women but the margin of error was larger in women. Women tended to inaccurately estimate their height and weight in favour of a lower BMI to a greater extent than men.[11] Many other studies have shown that women, when compared to men, misestimated their anthropometric data in such a way that it would lead to a lower BMI result.[4,6,8,11,14,32,34,35] Of the papers reviewed, only one study reported that women participants reported their BMI more accurately than men,[36] one study reported that men over-reported their BMI [17] and one study reported that men estimated their weight without significant bias.[37] The results of the current study are in line with previously published studies and revealed that weight was significantly underestimated and height was overestimated. As a result of this, BMI was significantly underestimated. In addition to this, our results were also similar to studies which found that women were more likely to underestimate their weight.

Table 5. Statistics for ROC curves of the BMI accuracy levels

		Male	Female
BMI accuracy	Positive	713	300
	Negative	245	202
Area		0.71	0.76
SE		0.021	0.022
p		0.000	0.000
95% CI		0.667 to 0.751	0.718 to 0.803

ROC: receiver operating characteristic, BMI: body mass index, SE: standard error, CI: confidence interval.

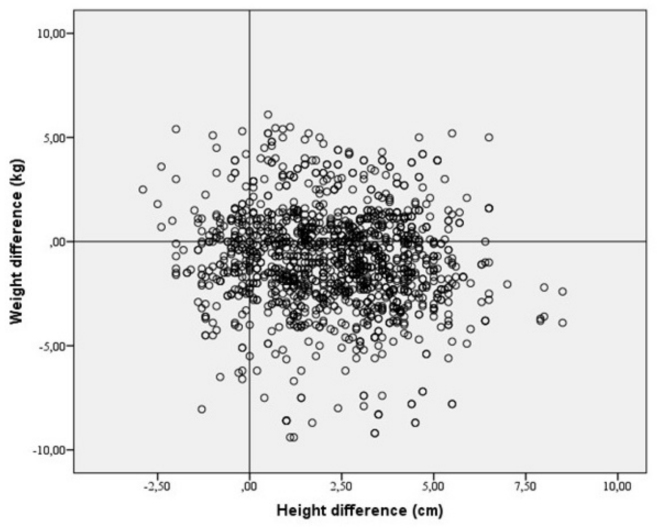

Figure 2. Map of estimation errors.

Table 6. Specificity, sensitivity and Kappa scores of self-reported data for BMI

	Men	Women	Overall
Specificity	99.9%	99.7%	99.8%
Sensitivity	69.5%	59.4%	65.9%
Kappa (SE)	0.719 (0.024)*	0.605 (0.036)*	0.678 (0.020)*

*p<0.001, BMI: body mass index, SE: standard error.

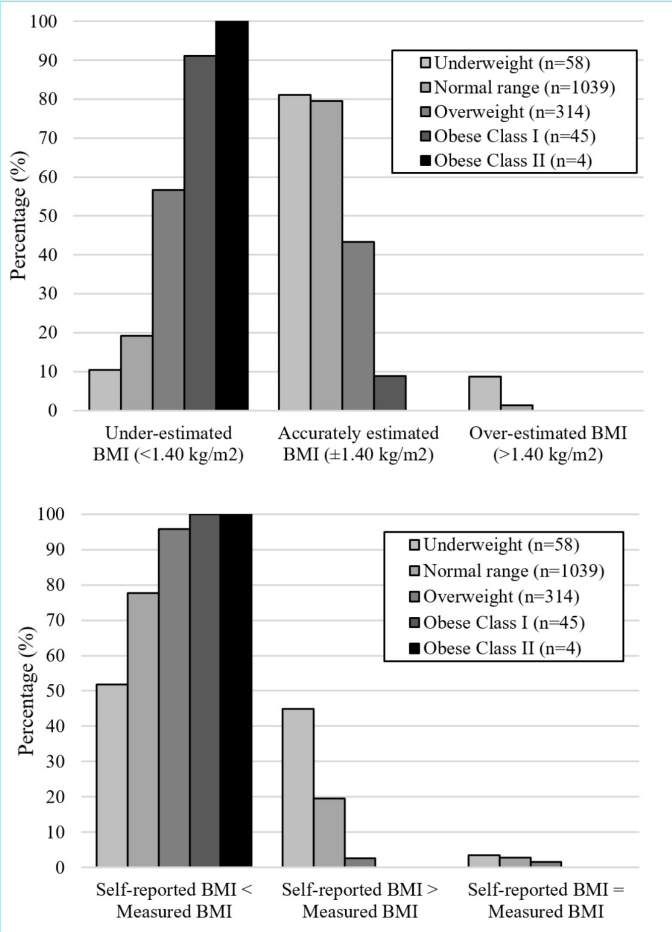

Figure 3. Estimation accuracy (top) and consistency (bottom) by BMI categories.

BMI: body mass index.

Engstrom et al.[38] reviewed the accuracy of self-report in women and it was found that overestimation was up to 7.6 cm in height and underestimation was up to 19 kg in weight. Engstrom et al.[38] reported that in all the studies reviewed, weight was underestimated while height was overestimated. These results are in line with the results of the current study.

It was previously reported that the reason for the tendency to underestimate weight might be that people weigh themselves with lighter clothes or without clothes in their private rooms compared with measurements taken when regularly dressed in public places such as a hospital or a clinic.[1,11] In addition to this, weighing with different scales might yield inconsistent results because of calibration inaccuracies. However, although this reason may contribute to an underestimation of weight, there is no strong evidence regarding it.[1] As the gap between the self-reported and measured weight is up to 20 kg, there might be another reason for this other than the calibration of the scales. In Turkish adults, it was revealed that there was a tendency to underestimate weight in both men and women. The main reason for this was thought to be the desire to be fit and thin, which is remarkably usual among women as has been reported.[2]

According to the results of a study carried out in Ireland, BMI misestimation was largely due to the underestimation of weight combined with the overestimation of height. It was also implied that as the level of BMI increased, both the prevalence and magnitude of self-reported BMI misestimation increased. It is believed that people misreport anthropometric data to depict a more socially desirable weight and height.[29] Some studies showed that the tendency to exhibit socially desired anthropometric ranges contributed to the misestimation of anthropometric data.[7,9]

Although "full-figured" women were desirable before the 1920s, this concept is clearly out of fashion in today's modern era and people have a desire to look more fit and thin. The reason for this transformation is not only due to societal concepts of how a person should look but also due to the goal to be thin which is promulgated by the fashion industry

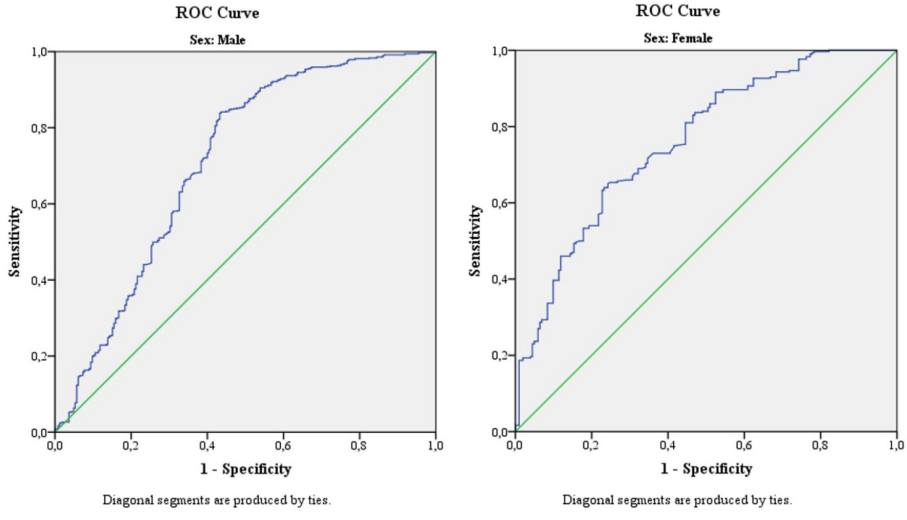

Figure 4. Receiver operating characteristics graph for BMI accuracy.

ROC: receiver operating characteristics, BMI: body mass index.

and reinforced by commercials.[3] It has been previously postulated that cultural pressures to be thin and tall cause people to misreport their anthropometric data towards more socially normative (i.e., desirable) values.[39] The bias revealed in this study for both genders may be due to the desire to look thinner and taller in order to comply with social norms. It has also been reported that there are results which support the view that heavier individuals desired to conform to social norms and attempted to appear thinner by underreporting their weight[40] more than their slimmer counterparts.[41]

Although the impact of age on the accuracy of self-reported BMI has been reported in some previous studies[17,31,42,43] and some studies revealed that aging affected the bias in self-report by leading to a tendency to over-report height and under-report weight,[36] no statistically significant differences between the age groups were found in the current study. The reason for this was thought to be that all the age groups overestimated their height and underestimated their weight.

The sociodemographic variables investigated in this study (level of education, marital status, and monthly income) and smoking habits were found to have no statistical influence on the accuracy of the self-reported anthropometric data although previous studies yielded different results regarding this.

In one study conducted on the American population, an association was reported between educational level and the degree of misreporting anthropometric data. The association between education and misreporting was explained by the fact that the concerns about excess weight were greater for those at higher socioeconomic and cultural levels.[42] Some other more recent studies revealed that sociodemographic variables including education had no association with misreporting height and weight.[2,15] In another study, no clear effect of the level of education on self-reported BMI accuracy was shown.[4] Craig and Adams[32] found that under-reporting was more likely to be among the well-educated but no supporting results were obtained in the current study. In a study conducted on Scottish adults,[11] no significant difference was found between the reported and measured data (including BMI) in terms of smoking habit or education level groups.

In the present study, no association between sociodemographic variables and self-reported anthropometric data was observed. This might be due to the fact that the desire to look thinner and taller in today's world is more common than ever before because of the wide utilization of web-based social networks and technology. Cultural and social pressures are postulated to have an effect on misreporting height and weight because social norms push people to look beyond how they actually look.[8,30,39] By being integrated into social networks and the internet, people see tall and fit people more frequently and the desire to look like them might contribute to bias in self-reported anthropometry.

Similar to the results of the studies conducted by Dekkers et al.[15] and Craig and Adams[32], the levels of agreement between BMI categorizations (self-reported and measured) were found to be substantial.

Bolton-Smith et al.[11] found the rate of specificity and sensitivity for estimates of obesity prevalence to be 83% and 96% (respectively, for men) and 89% and 97% (respectively, for women). In the current study, specificity for men was found to be 99.9% and 99.7% for women while sensitivity was 69.5% for men and 59.4% for women. Kappa values were 0.719 for men, 0.605 for women, and 0.678 in general. Similar to the findings of this study, Brener et al.[44] reported 99.2% specificity, 54.9% sensitivity, and a Kappa value of 0.77 for BMI classification.

It was reported in one study that the mean difference in the self-reported and measured height decreased as the measured height increased. Short (<173 cm for men, <160 cm for women) subjects reported their height at a sensitivity rate of 69% while the tall (>182 cm for men, >168 cm for women) subjects' rate was 94%. In contrast, weight was reported more accurately as the measured weight decreased in both men and women.[42]

The correlation between reported and measured BMI levels should be cautiously relied on. Despite the high correlation (r>0.9) between measured and self-reported BMI, misclassification of BMI level by self-report was shown to be about 30-40%.[45] In a study conducted in Australia, only 52% or the participants accurately reported their height while the rate of accurately reported weight was as low as 34%.[6] In a study conducted in Iran, the Kappa value for weight perception and measured weight was as low as 0.38 for women and 0.23 for men.[10]

In their work, Shiely et al.[29] reported that the Surveys of Lifestyle Attitudes and Nutrition 1998, 2002 and 2007 measurements revealed underreporting of BMI had statistically significantly increased over time across the three surveys (14%, 21%, 24% respectively). Specificity levels across the surveys did not change but sensitivity decreased in both the overweight and obese categories (75%, 68%, 66% for overweight and 80%, 64%, 53% for obese, respectively).

Although the severity of obesity is obvious, the size of the epidemic has usually been assessed by relying on self-reported anthropometric data.[8] It has been reported that self-reported height and weight could not be relied upon as an alternative to independent measurements in obesity assessments.[36] As obesity rates are threatening human health globally, accurate estimations of obesity prevalence are essential for setting effective health policies in order to prevent the obesity epidemic.[46]

CONCLUSION

The results of the current study suggest that the use of self-reported anthropometry in the Turkish population is questionable and measured data should be preferred to assess BMI. The subjects, both men and women, tended to overestimate their height and underestimate their weight, which led to biased BMIs. Such biases may lead to erroneous results with which to evaluate the obesity trend in Turkish adults. Women were more likely to deviate from their measured data in favour of their BMI categories than men. This general tendency to misclassification of BMI categories may prevent the government from setting appropriate policies to control obesity in Turkish adults. It should be kept in mind that self-reporting is a useful, easy, and cheap tool but it should not be relied on entirely to detect obesity prevalence. If a survey based on self-reported data is to be conducted, it would be good practice to measure a random subsample to investigate the magnitude and trajectory of any bias.

MAIN POINTS

- Turkish women were more prone to underestimate their weight and overestimate their height than Turkish men.
- Overestimation of height was found to reach up to 8.5 cm while underestimation in weight was about 9.4 kg.
- Self-reported anthropometry should be cautiously used in both personal and public obesity assessments and/or prevalence studies.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Researches Ethics Committee of Hitit University (approval number: 2018-07).

Informed Consent: The subjects were informed about the aim of this study and their written consent was obtained.

Peer-review: Externally peer-reviewed.

DISCLOSURES

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RESEARCH ARTICLE

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Perception of Smile Aesthetics by Dental Professionals and Laypeople of Different Age and Gender in Canine Substitution

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Abstract

BACKGROUND/AIMS: This study aimed to evaluate the effect of different smile patterns that may occur as a result of canine substitution for the treatment of missing lateral incisor(s) on the esthetic perception in patients of different age groups, sex, and profession (dental professionals and laypeople).

MATERIALS AND METHODS: The frontal extraoral photographs of a 28-year-old female patient were digitally modified using an image editing software program (Photoshop CC; Adobe Corp). Eight photographs were produced by simulating canine substitution with altered teeth and gingival levels. A total of 713 (317 dental professionals and 396 laypeople) respondents participated in an online survey. A numeric rating scale was used, with "0" representing the least attractive and "10", the most attractive. Kruskal-Wallis and Mann-Whitney U tests were used for comparison. Bonferroni correction was used to check type1 errors in all possible multiple comparisons.

RESULTS: In the group of dental professionals and laypeople aged 36-45, females had lower appreciation percentages compared to males ($p<0.000625$). Dental professionals had lower appreciation percentages than laypeople ($p<0.00056$). Male dental professionals in the 26-35 age group had lower appreciation percentages compared to the 36-45, 46-55, and 56-65 age groups ($p<0.00156$).

CONCLUSION: While reshaping canines as lateral incisor teeth, the participants' age, sex, and whether the participant was a dentist, affected the esthetic perception. However, gingival level differences and whether the treatment was symmetrical did not cause any difference in terms of esthetic perception for any of the groups.

Keywords: Esthetics, smile design, canine substitution, lateral incisor agenesis

INTRODUCTION

Improving dental esthetics leads to a substantial increase in the quality of life underlying the psychosocial importance of a pleasing smile.[1] The analysis of smile esthetics is complicated because it is difficult to standardize a practical model and to change the variables of interest.[2] Additionally, it becomes more difficult to provide esthetics in the presence of dental anomalies.

The most common craniofacial developmental anomaly in humans is agenesis of the teeth. It is a number disorder specified by the absence of single or multiple teeth, which can be attributed to genetic or external factors[3-6] or linked to syndromes.[3,6] Many studies have attempted to explain the prevalence of hypodontia over the past few years. Depending on the ethnic group, the maxillary lateral incisors may have the highest[5] or second-highest[7] incidences. The prevalence of maxillary lateral incisor agenesis ranges from 0.8%[8] to 2%[9] in which females are

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more affected than males.[10] A meta-analysis showed the prevalence of bilateral agenesis of maxillary lateral incisors to be between 50.9% and 57%,[4] while other studies have found unilateral agenesis to be more extensive.[9,10]

In clinical practice, the absence of the lateral incisor can cause esthetic, periodontal, and functional issues. These deficiencies compromise smile harmony and result in an unattractive facial appearance.[3] There are two main treatment options for maxillary lateral incisor agenesis: orthodontic space closure with canine substitution or orthodontic space opening with prosthetic replacement.[7,11-14] A recent systematic study has confirmed orthodontic space closure improved periodontal and esthetic parameters.[13] Several clinical factors, such as age, sagittal occlusion, facial profile, presence or absence of crowding in both dental arches and tooth morphology,[7,11,12] or patient-related factors, such as financial capabilities and esthetic preferences, may influence the treatment preference.[15] The more a canine tooth's form, size, color, and gingival margin deviates from that of a lateral incisor, the more difficult it is to modify it to look like one.[16]

It is important to remember that esthetic perception may differ between dentists and patients.[17] Therefore, a consensus on the best care for the patient's practical and esthetic needs has to be reached, and this should include not only dentists' but also patients' interpretations.[3,18] Some esthetic deficiencies, such as the proportion and position of the individual teeth and gingival tissue asymmetries, may often not be noticeable to laypeople, which may question the real need for esthetic treatments. This study aimed to evaluate the effect of different smile patterns which may occur as a result of canine substitution for the treatment of missing lateral incisor(s) on esthetic perception in patients of different age groups, genders, and professions (dental professionals and laypeople). The null hypothesis was that there was no difference in esthetic perception among the different groups of profession, age, and gender.

MATERIALS AND METHODS

This study was approved by Başkent University Institutional Review Board (approval number: 94603339/050.01.08.01-04; project number: D-KA20/39, date: 08.12.2020). The frontal extraoral photographs of a 28-year-old female were used to conduct the present study. She provided informed consent for the use of her images in the survey and publication of this manuscript. The patient had no orthodontic treatment records, and her smile showed unrestored and healthy maxillary anterior teeth. This patient's dental appearance was rated as highly attractive based on the subjective concepts of ideal esthetic criteria mentioned in the literature.[19]

A digital camera with a tripod and macro 60 mm objective lens (10 megapixels; Canon XTI Rebel, Japan) was used to produce distinct photographs which showed the patient's face's inferior third, including the teeth, gingiva, and lips. All photographs were taken at a distance of one meter, with the subject standing at the same height as the photographer. The participant was instructed to maintain a natural head posture while focusing their eyes on an imaginary point at eye level. The original photograph was modified using Adobe Photoshop CC software (Adobe Systems Inc., San Francisco, CA, USA); however, the mandibular arch was not altered.

The photograph was altered in the anterior region of the maxillary arch, with varying compositions of distinct forms and gingival contours of the lateral teeth. Changes were made to simulate individualized repositioning of the canine in the left or both sides in the place of the lateral incisor.

The groups of figures were divided as follows: original (reference) smile image with no canine substitution (Figure 1), original canine as lateral incisor, substituted unilaterally, original canine gingival level (Figure 2); original canine as lateral incisor, substituted unilaterally, lateral gingival level (Figure 3); reshaped canine as lateral incisor, substituted unilaterally, original canine gingival level (Figure 4); reshaped canine as lateral incisor, substituted unilaterally, lateral gingival level (Figure 5); original canine as lateral incisor, substituted bilaterally, original canine gingival level (Figure 6); original canine as lateral incisor, substituted bilaterally, lateral gingival level (Figure 7); reshaped canine as lateral

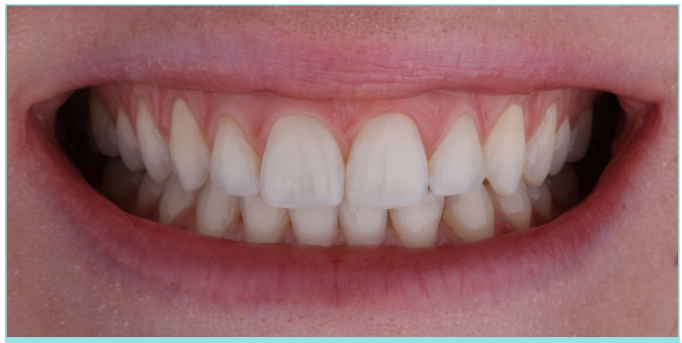

Figure 1. Original (reference) smile image with no canine substitution.

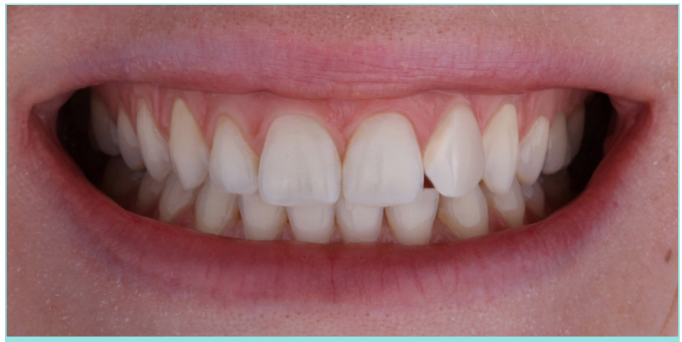

Figure 2. Original canine as lateral incisor, substituted unilaterally, original canine gingival level.

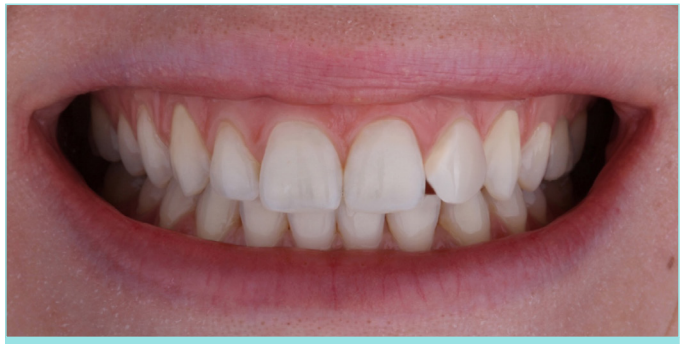

Figure 3. Original canine as lateral incisor, substituted unilaterally, lateral gingival level.

incisor, substituted bilaterally, original canine gingival level (Figure 8); reshaped canine as lateral incisor, substituted bilaterally, lateral gingival level (Figure 9).

All participants were informed that single or bilateral maxillary lateral incisor agenesis is a very common dental and esthetic problem. Positioning the canine in place of the lateral incisor is one of the treatment alternatives. This study aimed to evaluate the effect on esthetic perception of different smile models which may occur as a result of positioning the canine instead of the lateral incisor. For each of the nine smile images, participants filled out demographic details and responded to the question, "How do you evaluate the overall esthetic of this smile?" A numeric rating scale (NRS) with 0 representing "the least attractive" and 10 representing "the most attractive" was used to answer the questions.

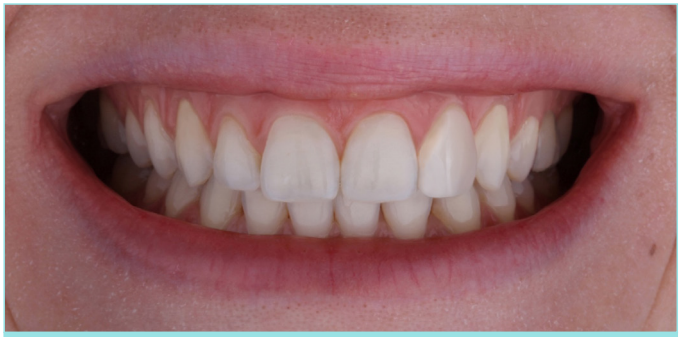

Figure 4. Reshaped canine as lateral incisor, substituted unilaterally, original canine gingival level.

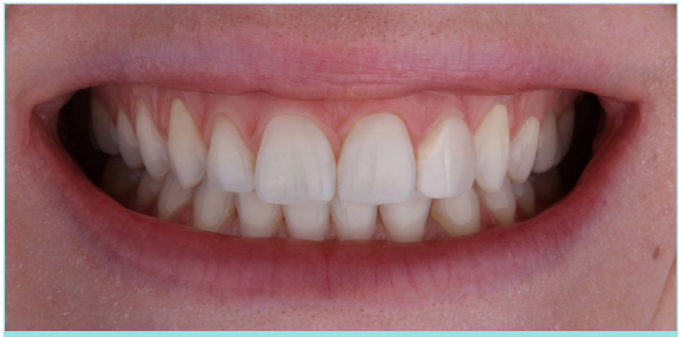

Figure 5. Reshaped canine as lateral incisor, substituted unilaterally, lateral gingival level.

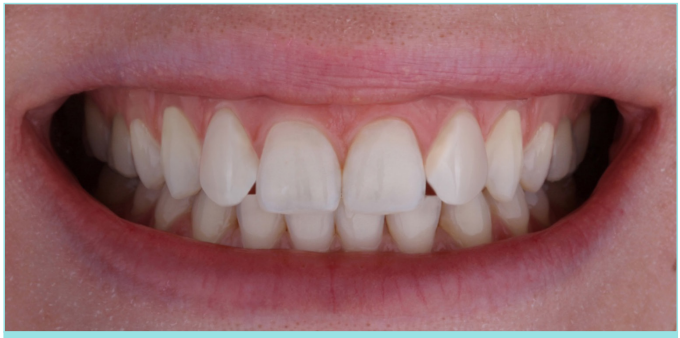

Figure 6. Original canine as lateral incisor, substituted bilaterally, original canine gingival level.

The 713 people who answered the survey were either dentists, dental students, or laypeople. The age range of the entire sample was 20 to 65 years, and it was divided into five age groups: 20-25, 26-35, 36-45, 46-55, 56-65 years.[20]

The survey was prepared on the internet, and the participants were provided with a link (docs.google.com/forms) to access the survey. The survey was communicated to the participants via social media.

Statistical Procedures

The Kolmogorov-Smirnov test was used to determine whether the distribution of continuous and discrete numerical variables was close to normal and whether the assumption of homogeneity of variances was achieved with the Levene test. Descriptive statistics: The median for

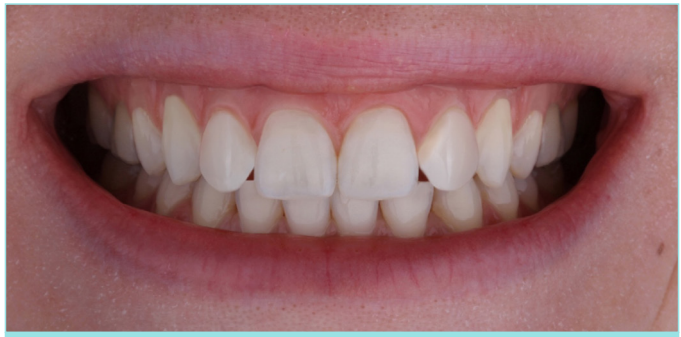

Figure 7. Original canine as lateral incisor, substituted bilaterally, lateral gingival level.

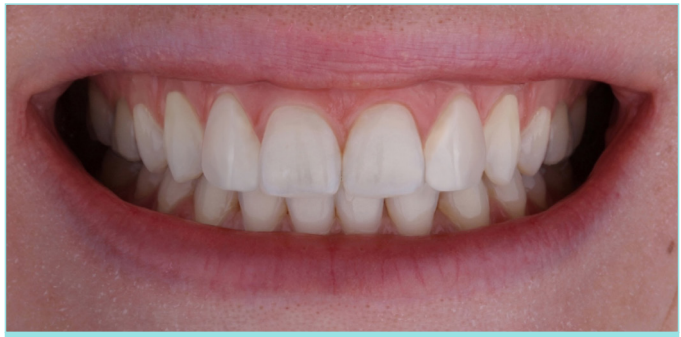

Figure 8. Reshaped canine as lateral incisor, substituted bilaterally, original canine gingival level.

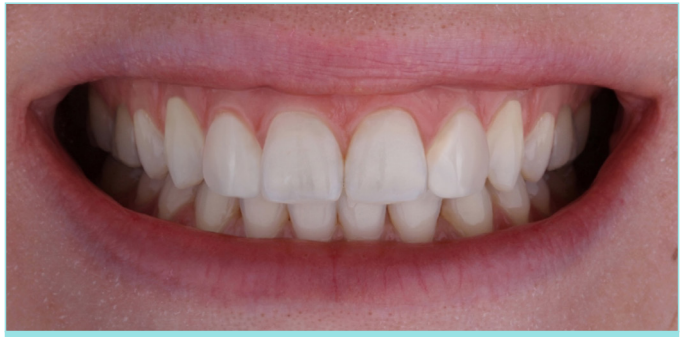

Figure 9. Reshaped canine as lateral incisor, substituted bilaterally, lateral gingival level.

continuous and discrete numeric variables (25^{th}-75^{th}) was expressed as a percentage, while categorical variables were expressed as numbers (n) and percentages (%).

The Friedman test was used the examine the statistical difference in terms of esthetic perception levels among different smile models within each subgroup when the age groups, sex, and professional groups of the participants were held constant. If the results of the Friedman test statistics were found to be significant, the smile model(s) which caused the difference was determined using the Dunn-Bonferroni test.

The Mann-Whitney U test was used to examine whether gender and type of profession were effective on the level of esthetic perception according to smile models. The Kruskal-Wallis test was used to evaluate the statistical difference in esthetic perception levels according to age groups. If the Kruskal-Wallis test results were found to be significant, the age groups that caused the difference were determined using the Dunn-Bonferroni test.

Percentage changes in the esthetic perception level in other smile models according to the reference smile model were calculated using the following formula:

Percentage change in esthetic perception = [(esthetic perception score of the examined smile model-esthetic perception score of the reference model)/esthetic perception score of the reference model] × 100.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (version 17.0; IBM Corporation, Armonk, NY, USA). Unless otherwise stated, results with $p<0.05$ were considered statistically significant. However, Bonferroni correction was used to check type 1 error in all possible multiple comparisons.

RESULTS

Table 1 presents the demographic information of the participants. Table 2 shows the in-group comparisons made in terms of the level of appreciation of the figures according to the participants' age, gender, and professional groups.

Table 3 shows intergroup comparisons made in terms of the level of appreciation of the figures according to age, gender, and professional groups. There was no statistically significant difference between males and females in terms of their appreciation levels of each figure examined by either dental professionals or laypeople, within each age group ($p>0.00056$). In the groups of males and females aged 26-35 and 36-45, dental professionals had lower appreciation levels compared to laypeople ($p<0.00056$). Male dental professionals in the 56-65 age group had higher appreciation levels compared to the 26-35 and 36-45 age groups ($p<0.0014$). Female dental professionals in the 46-55 age group had higher appreciation levels compared to the 36-45 age group ($p<0.0014$).

Table 1. Demographic information of study participants

	Dental professionals	Laypeople	Total
Age groups			
20-25	50 (15.8%)	66 (16.7%)	116 (16.3%)
26-35	77 (24.3%)	90 (22.7%)	167 (23.4%)
36-45	96 (30.2%)	111 (28.0%)	207 (29.0%)
46-55	49 (15.5%)	72 (18.2%)	121 (17.0%)
56-65	45 (14.2%)	57 (14.4%)	102 (14.3%)
Gender			
Male	133 (42.0%)	186 (47.0%)	319 (44.7%)
Female	184 (58.0%)	210 (53.0%)	394 (55.3%)
Total	317 (44.5%)	396 (55.5%)	713 (100.0%)

Table 4 shows comparisons between age, gender, and professional groups in terms of their appreciation percentages of other figures evaluated according to the reference figure. In the group of dental professionals and laypeople aged 36-45, females had lower appreciation percentages compared to males ($p<0.000625$). Male and female dental professionals had lower appreciation percentages compared to laypeople ($p<0.00056$). Male and female dental professionals in the 26-35 age group had lower appreciation percentages compared to the other age groups ($p<0.00156$).

In all remaining possible multiple comparisons, no statistically significant difference was found between the groups ($p<0.000625$).

DISCUSSION

This study aimed to reveal the esthetic perception of dental professionals and laypeople with consideration to their age and sex. To minimize anatomical differences between the canines and maxillary lateral incisors, clinical situations were simulated by changing the canine shape and gingival contour bilaterally and unilaterally. The results showed that the null hypothesis that there was no difference in aesthetic perception among different groups of age, sex and profession was rejected.

When the attractiveness of a smile was examined by gender, significant differences were observed among the dental professionals and laypeople in the 36-45 age group. The esthetic perception percentage of the female groups was significantly lower in both groups. However, no statistically significant differences were noted among the other groups (Table 4). This is partially in agreement with the findings of previous studies showing that there are differences in esthetic perception between males and females.[21,22] In the literature, there are also contradicting results, while the female group was more critical in some studies,[2,21] Schabel et al.[23] received more rigid assessments from the male group in their study. According to the results of the current study, although the female group pays more attention to details than males when evaluating smile photographs of some specific groups, it is still unclear whether there is a relationship between gender and esthetic smile perception.

When the attractiveness of smile was examined in terms of profession, significant differences were observed among the male and female dental professionals compared to the laypeople in the group aged 36-45 which showed significantly lower appreciation percentages of all figures with respect to the reference figure. Female dental professionals, when compared to the female laypeople in the groups aged 26-35 and 46-55, gave significantly lower appreciation percentages to most figures in comparison to the reference figure (Table 4). Similar to the results of this study, Roden-Johnson et al.[24] found that dentists are stricter evaluators than laypeople. This result can be rationalized by the fact that dentists are professionals, and thus can easily detect small differences in a

Table 2. Esthetic perception levels of different smile models according to age, gender and professional groups - in-group comparisons

Age groups						
		20-25	**26-35**	**36-45**	**46-55**	**56-65**
Male dental professionals	Figure 1	8.0 (7.0-9.0)	8.0 (7.5-9.0)	8.0 (7.0-9.0)	9.0 (7.8-9.3)	9.0 (9.0-10.0)
	Figure 2	3.0 (3.0-6.0)[1]	3.0 (2.0-5.0)[1]	4.0 (3.0-5.0)[1]	5.5 (4.0-7.3)[1]	5.0 (4.0-6.0)[1]
	Figure 3	3.0 (3.0-5.0)[1]	3.0 (2.0-5.5)[1]	5.0 (3.0-5.0)[1]	5.5 (4.0-7.0)[1]	5.0 (4.0-6.0)[1]
	Figure 4	5.0 (4.0-8.0)	5.0 (3.0-6.5)[1]	6.0 (5.0-6.0)[1,2,3]	6.0 (5.8-7.5)	7.0 (5.5-8.0)
	Figure 5	7.0 (6.0-8.0)	5.0 (3.5-6.0)[1]	6.0 (5.0-7.0)[2,3]	6.5 (6.0-8.3)	8.0 (6.5-8.0)[2,3]
	Figure 6	5.0 (3.0-6.0)[1]	4.0 (1.0-6.0)[1]	4.0 (3.0-6.0)[1,5]	6.0 (5.0-7.3)[1]	5.0 (4.0-7.0)[1,5]
	Figure 7	5.0 (3.0-7.0)	3.0 (2.0-5.5)[1]	4.0 (3.0-6.0)[1,4,5]	6.0 (5.8-8.0)[1]	6.0 (4.0-6.5)[1,5]
	Figure 8	7.0 (6.0-8.0)[2,3]	6.0 (4.0-8.0)[3,6,7]	6.0 (6.0-7.3)[2,3,6,7]	7.5 (6.0-9.3)	8.0 (7.0-8.0)[2,3,6,7]
	Figure 9	8.0 (7.0-10.0)[2,3,6,7]	6.0 (5.0-8.0)[2,3,6,7]	6.0 (5.8-8.0)[2,3,6,7]	9.0 (6.8-9.3)[2,3]	8.0 (8.0-9.0)[2,3,6,7]
Female dental professionals	Figure 1	8.0 (7.0-9.0)	8.5 (7.0-10.0)	9.0 (8.0-9.0)	9.0 (8.0-10.0)	8.0 (7.0-10.0)
	Figure 2	5.0 (3.0-6.0)[1]	4.0 (2.0-5.0)[1]	4.0 (4.0-5.0)[1]	5.0 (4.0-7.0)[1]	5.0 (4.0-6.0)[1]
	Figure 3	5.0 (3.0-5.0)[1]	4.0 (2.0-5.0)[1]	5.0 (4.0-5.0)[1]	5.0 (4.0-6.0)[1]	5.0 (4.0-6.0)[1]
	Figure 4	5.0 (4.0-6.0)[1]	5.0 (4.0-7.0)[1]	5.0 (5.0-6.0)[1]	6.0 (5.0-7.0)[1]	6.0 (4.3-7.0)
	Figure 5	6.0 (5.0-8.0)	6.0 (4.0-7.0)[1,2]	6.0 (5.0-7.0)[1,2,3]	6.0 (5.0-8.0)[1]	6.0 (4.3-7.0)
	Figure 6	4.0 (2.0-6.0)[1,5]	3.0 (2.0-5.0)[1,5]	4.0 (4.0-5.0)[1,5]	5.0 (3.0-7.0)[1]	5.0 (4.0-6.0)[1]
	Figure 7	4.0 (2.0-5.0)[1,5]	3.0 (2.0-5.0)[1,5]	4.0 (3.0-5.0)[1,5]	5.0 (3.0-7.0)[1]	5.0 (3.3-6.0)[1]
	Figure 8	6.0 (4.0-8.0)	6.0 (4.0-8.0)[2,3,6,7]	7.0 (5.8-7.0)[1,2,3,6,7]	8.0 (6.0-10.0)[2,3,6,7]	7.5 (5.3-9.0)[2,3,6,7]
	Figure 9	7.0 (5.0-9.0)[2,3,6,7]	7.0 (6.0-8.8)[2,3,4,6,7]	8.0 (7.0-8.0)[2,3,4,6,7]	8.0 (6.0-10.0)[2,3,4,6,7]	8.0 (6.3-9.0)[2,3,6,7]
Male laypeople	Figure 1	8.0 (7.0-8.8)	9.0 (8.0-9.3)	8.0 (7.0-8.3)	8.0 (7.0-9.0)	8.0 (6.0-9.0)
	Figure 2	7.0 (5.0-7.8)	6.5 (5.0-8.0)[1]	7.0 (5.0-7.0)[1]	6.0 (6.0-8.0)[1]	7.0 (5.0-7.0)
	Figure 3	6.0 (4.3-7.0)[1]	6.0 (5.0-7.0)[1]	7.0 (5.0-7.0)[1]	6.0 (5.0-8.0)	7.0 (5.0-7.0)
	Figure 4	8.0 (5.3-8.0)	8.0 (7.0-9.0)	8.0 (7.8-9.0)[2,3]	8.0 (5.0-9.0)	8.0 (6.0-9.0)
	Figure 5	7.0 (6.0-9.0)	8.0 (7.0-9.0)[3]	8.0 (7.0-8.0)[2]	8.0 (6.0-9.0)	8.0 (5.0-9.0)
	Figure 6	6.0 (4.0-7.0)	6.0 (4.8-8.0)[1,4,5]	6.0 (5.0-7.0)[1,4,5]	6.0 (5.0-8.0)[1,5]	6.0 (5.0-7.0)
	Figure 7	6.0 (4.0-7.0)[1,4]	6.0 (4.0-7.3)[1,4,5]	6.0 (5.0-7.0)[1,4,5]	6.0 (5.0-8.0)[1,5]	6.0 (5.0-7.0)
	Figure 8	8.0 (6.0-8.0)[7]	8.0 (8.0-9.3)[2,3,6,7]	8.0 (7.8-9.0)[2,3,6,7]	8.0 (6.0-9.0)[7]	8.0 (5.0-9.0)[2,3]
	Figure 9	7.0 (6.0-8.8)[7]	8.5 (7.0-10.0)[2,3,6,7]	8.0 (7.0-9.0)[2,3,6,7]	8.0 (6.0-9.0)[2,6,7]	8.0 (6.0-9.0)[2,3,6,7]
Female laypeople	Figure 1	8.0 (7.0-9.0)	8.0 (6.3-10.0)	8.0 (7.0-10.0)	8.0 (6.0-10.0)	8.0 (7.0-9.0)
	Figure 2	6.0 (4.0-7.3)[1]	6.0 (4.0-7.0)[1]	6.0 (5.0-7.5)[1]	6.0 (5.0-8.0)	6.0 (5.0-7.0)[1]
	Figure 3	6.0 (3.0-7.0)[1]	5.0 (4.0-7.0)[1]	6.0 (5.0-7.0)[1]	6.0 (5.0-7.0)[1]	6.0 (4.0-7.3)[1]
	Figure 4	8.0 (5.8-9.0)[2,3]	7.0 (6.0-8.0)[3]	7.0 (6.0-9.0)[2,3]	8.0 (5.0-9.0)[3]	7.0 (5.0-8.0)
	Figure 5	8.0 (6.8-9.0)[2,3]	7.0 (6.0-8.0)[2,3]	7.0 (6.0-8.5)[2,3]	7.0 (6.0-9.0)[3]	7.0 (6.0-8.3)
	Figure 6	5.5 (4.0-7.3)[1,4,5]	6.0 (5.0-7.0)[1,4,5]	6.0 (5.0-7.0)[1,4,5]	7.0 (5.0-8.0)	6.0 (5.0-8.0)[1]
	Figure 7	5.5 (4.0-7.0)[1,4,5]	6.0 (4.0-7.0)[1,4,5]	6.0 (5.0-7.0)[1,4,5]	6.0 (5.0-8.0)	5.5 (5.0-7.0)[1]
	Figure 8	8.0 (6.0-9.0)[3,7]	8.0 (6.0-9.0)[2,3,6,7]	8.0 (7.0-9.0)[2,3,6,7]	8.0 (6.0-9.0)[3]	8.0 (7.0-9.0)[2,3,7]
	Figure 9	8.5 (7.0-9.0)[2,3,6,7]	8.0 (6.0-9.0)[2,3,6,7]	9.0 (7.0-9.5)[2,3,6,7]	8.0 (6.0-9.0)[3]	7.5 (7.0-8.3)

Descriptive statistics; The median (25th-75th) are shown as percentages. The results were considered statistically significant for p<0.0025 according to the Bonferroni correction. [1]The difference with Figure 1 was statistically significant (p<0.0025). [2]The difference with Figure 2 was statistically significant (p<0.0025). [3]The difference with Figure 3 was statistically significant (p<0.0025). [4]The difference with Figure 4 was statistically significant (p<0.001). [5]The difference with Figure 5 was statistically significant (p<0.0025). [6]The difference with Figure 6 was statistically significant (p<0.0025). [7]The difference with Figure 7 was statistically significant (p<0.001).

smile.[22,23] On the other hand, Krishnan et al.[25] reported that dentists and laypeople were equally critical in their judgment.

This study also focused on whether age is an important factor in esthetic perception. For the male dental professional groups aged 36-45, 46-55, and 56-65, the esthetic perception percentage of some figures was significantly higher than the 26-35 age group. For the male laypeople group aged 36-45, the esthetic perception percentage of some figures is significantly higher than the 26-35 age group. Apart from these groups, the esthetic perception percentage was not affected by age (Table 4). This result is partially in agreement with the findings of previous studies.[26-28] Pithon et al.[26] reported that younger laypeople are more critical of dental esthetics than older people. A similar finding was observed in a study[27] which focused on the definition of smile attractiveness and its esthetic criteria differences, in which younger evaluators were more critical when evaluating smiles with diastema. Another study[28] also reported that age affects smile perception. On the other hand, Kokich et al.[22] found that age did not affect esthetic

Table 3. Esthetic perception levels of different smile models according to age, gender and profession groups - comparisons between groups

Age groups						
		20-25	26-35	36-45	46-55	56-65
Male dental professionals	Figure 1	8.0 (7.0-9.0)	8.0 (7.5-9.0)	8.0 (7.0-9.0)	9.0 (7.8-9.3)	9.0 (9.0-10.0)[A]
	Figure 2	3.0 (3.0-6.0)	3.0 (2.0-5.0)[A]	4.0 (3.0-5.0)[A]	5.5 (4.0-7.3)	5.0 (4.0-6.0)
	Figure 3	3.0 (3.0-5.0)	3.0 (2.0-5.5)[A]	5.0 (3.0-5.0)[A]	5.5 (4.0-7.0)	5.0 (4.0-6.0)
	Figure 4	5.0 (4.0-8.0)	5.0 (3.0-6.5)[A]	6.0 (5.0-6.0)[A]	6.0 (5.8-7.5)	7.0 (5.5-8.0)[1]
	Figure 5	7.0 (6.0-8.0)	5.0 (3.5-6.0)[A]	6.0 (5.0-7.0)[A]	6.5 (6.0-8.3)	8.0 (6.5-8.0)[1]
	Figure 6	5.0 (3.0-6.0)	4.0 (1.0-6.0)[A]	4.0 (3.0-6.0)[A]	6.0 (5.0-7.3)[1]	5.0 (4.0-7.0)
	Figure 7	5.0 (3.0-7.0)	3.0 (2.0-5.5)	4.0 (3.0-6.0)[A]	6.0 (5.8-8.0)[1]	6.0 (4.0-6.5)
	Figure 8	7.0 (6.0-8.0)	6.0 (4.0-8.0)[A]	6.0 (6.0-7.3)[A]	7.5 (6.0-9.3)	8.0 (7.0-8.0)
	Figure 9	8.0 (7.0-10.0)	6.0 (5.0-8.0)[A]	6.0 (5.8-8.0)[A]	9.0 (6.8-9.3)	8.0 (8.0-9.0)[1,2]
Female dental professionals	Figure 1	8.0 (7.0-9.0)	8.5 (7.0-10.0)	9.0 (8.0-9.0)	9.0 (8.0-10.0)	8.0 (7.0-10.0)
	Figure 2	5.0 (3.0-6.0)	4.0 (2.0-5.0)[B]	4.0 (4.0-5.0)[B]	5.0 (4.0-7.0)[2]	5.0 (4.0-6.0)
	Figure 3	5.0 (3.0-5.0)	4.0 (2.0-5.0)	5.0 (4.0-5.0)[B]	5.0 (4.0-6.0)	5.0 (4.0-6.0)
	Figure 4	5.0 (4.0-6.0)[B]	5.0 (4.0-7.0)[B]	5.0 (5.0-6.0)[B]	6.0 (5.0-7.0)	6.0 (4.3-7.0)
	Figure 5	6.0 (5.0-8.0)	6.0 (4.0-7.0)	6.0 (5.0-7.0)[B]	6.0 (5.0-8.0)	6.0 (4.3-7.0)
	Figure 6	4.0 (2.0-6.0)	3.0 (2.0-5.0)[B]	4.0 (4.0-5.0)[B]	5.0 (3.0-7.0)	5.0 (4.0-6.0)
	Figure 7	4.0 (2.0-5.0)	3.0 (2.0-5.0)[B]	4.0 (3.0-5.0)[B]	5.0 (3.0-7.0)	5.0 (3.3-6.0)
	Figure 8	6.0 (4.0-8.0)	6.0 (4.0-8.0)	7.0 (5.8-7.0)[B]	8.0 (6.0-10.0)	7.5 (5.3-9.0)
	Figure 9	7.0 (5.0-9.0)	7.0 (6.0-8.8)	8.0 (7.0-8.0)	8.0 (6.0-10.0)	8.0 (6.3-9.0)
Male laypeople	Figure 1	8.0 (7.0-8.8)	9.0 (8.0-9.3)	8.0 (7.0-8.3)	8.0 (7.0-9.0)	8.0 (6.0-9.0)[A]
	Figure 2	7.0 (5.0-7.8)	6.5 (5.0-8.0)[A]	7.0 (5.0-7.0)[A]	6.0 (6.0-8.0)	7.0 (5.0-7.0)
	Figure 3	6.0 (4.3-7.0)	6.0 (5.0-7.0)[A]	7.0 (5.0-7.0)[A]	6.0 (5.0-8.0)	7.0 (5.0-7.0)
	Figure 4	8.0 (5.3-8.0)	8.0 (7.0-9.0)[A]	8.0 (7.8-9.0)[A]	8.0 (5.0-9.0)	8.0 (6.0-9.0)
	Figure 5	7.0 (6.0-9.0)	8.0 (7.0-9.0)[A]	8.0 (7.0-8.0)[A]	8.0 (6.0-9.0)	8.0 (5.0-9.0)
	Figure 6	6.0 (4.0-7.0)	6.0 (4.8-8.0)[A]	6.0 (5.0-7.0)[A]	6.0 (5.0-8.0)	6.0 (5.0-7.0)
	Figure 7	6.0 (4.0-7.0)	6.0 (4.0-7.3)	6.0 (5.0-7.0)[A]	6.0 (5.0-8.0)	6.0 (5.0-7.0)
	Figure 8	8.0 (6.0-8.0)	8.0 (8.0-9.3)[A]	8.0 (7.8-9.0)[A]	8.0 (6.0-9.0)	8.0 (5.0-9.0)
	Figure 9	7.0 (6.0-8.8)	8.5 (7.0-10.0)[A]	8.0 (7.0-9.0)[A]	8.0 (6.0-9.0)	8.0 (6.0-9.0)
Female laypeople	Figure 1	8.0 (7.0-9.0)	8.0 (6.3-10.0)	8.0 (7.0-10.0)	8.0 (6.0-10.0)	8.0 (7.0-9.0)
	Figure 2	6.0 (4.0-7.3)	6.0 (4.0-7.0)[B]	6.0 (5.0-7.5)[B]	6.0 (5.0-8.0)	6.0 (5.0-7.0)
	Figure 3	6.0 (3.0-7.0)	5.0 (4.0-7.0)	6.0 (5.0-7.0)[B]	6.0 (5.0-7.0)	6.0 (4.0-7.3)
	Figure 4	8.0 (5.8-9.0)[B]	7.0 (6.0-8.0)[B]	7.0 (6.0-9.0)[B]	8.0 (5.0-9.0)	7.0 (5.0-8.0)
	Figure 5	8.0 (6.8-9.0)	7.0 (6.0-8.0)	7.0 (6.0-8.5)[B]	7.0 (6.0-9.0)	7.0 (6.0-8.3)
	Figure 6	5.5 (4.0-7.3)	6.0 (5.0-7.0)[B]	6.0 (5.0-7.0)[B]	7.0 (5.0-8.0)	6.0 (5.0-8.0)
	Figure 7	5.5 (4.0-7.0)	6.0 (4.0-7.0)[B]	6.0 (5.0-7.0)[B]	6.0 (5.0-8.0)	5.5 (5.0-7.0)
	Figure 8	8.0 (6.0-9.0)	8.0 (6.0-9.0)	8.0 (7.0-9.0)[B]	8.0 (6.0-9.0)	8.0 (7.0-9.0)
	Figure 9	8.5 (7.0-9.0)	8.0 (6.0-9.0)	9.0 (7.0-9.5)	8.0 (6.0-9.0)	7.5 (7.0-8.3)

Descriptive statistics; the median (25^{th}-75^{th}) are shown as percentages. [1]When the gender and profession groups were held constant, the difference was statistically significant compare to 26-35 age group ($p<0.0014$). [2]When the gender and profession group were held constant, the difference was statistically significant compare to 36-45 age group ($p<0.0014$). [A]When the age group was held constant, the difference between dental professionals and laypeople group was statistically significant in male groups ($p<0.00056$). [B]When the age group was held constant, the difference between dental professionals and laypeople group was statistically significant in female groups ($p<0.00056$).

perception. This is also partially in agreement with the results of the current study since dental professionals' years of practical knowledge and laypeople evaluators' age did not affect the esthetic perception in female groups. Additionally, it is important to emphasize that younger evaluators in the male group were more critical. Therefore, it is still unclear whether there is a relationship between age and esthetic smile perception.

Space closure with canine repositioning in place of the absence of the lateral incisor might be the best treatment alternative.[14] However, certain canine features must be altered for these teeth to resemble the missing lateral incisors in terms of esthetic appearance. Therefore, this study also focused on camouflaging the canine to mimic the appearance of a lateral incisor, as shown in Figures 4, 5, 8, and 9. When the attractiveness of the smile was examined according to the tooth form in all groups, except for male dentists aged 46-55 and female laypeople

Table 4. Comparisons of esthetic perception (%) according to the reference smile image among the groups of age, gender and profession

Age groups						
		20-25	26-35	36-45	46-55	56-65
Male dental professionals	Figure 2	−57.1 (−66.7 - −28.6)	−57.1 (−75.0 - −33.3)^{A}	−44.4 (−51.4 - −39.4)^{A}	−35.4 (−42.9 - −21.7)	−44.4 (−55.6 - −31.7)^{A}
	Figure 3	−57.1 (−66.7 - −37.5)^{A}	−62.5 (−75.0 - −33.3)^{A}	−43.7 (−50.0 - −33.3)^{A}	−35.4 (−42.9 - −22.2)	−44.4 (−52.8 - −33.3)^{A}
	Figure 4	−33.3 (−42.9 - 0.0)	−44.4 (−62.5 - −22.2)^{A}	−28.6 (−37.5 - −11.1)^{A}	−23.6 (−33.3 - −11.9)	−22.2 (−36.7 - −11.8)^{A}
	Figure 5	−14.3 (−25.0 - 0.0)	−37.5 (−59.0 - −25.0)^{A,1}	−22.2 (−25.0 - 0.0)^{A,a,2}	−14.3 (−33.3 - −10.8)^{A}	-14.3 (−27.5 - −5.0)^{2}
	Figure 6	−33.3 (−62.5 - −14.3)	−55.6 (−86.6 - −29.2)^{A}	−40.0 (−50.0 - −33.3)^{A}	−28.6 (−33.3 - −20.0)^{2}	−33.3 (−55.6 - −26.8)^{A}
	Figure 7	−40.0 (−62.5 - −10.0)	−62.5 (−75.0 - −37.5)^{A}	−42.9 (−56.0 - −33.3)^{A}	−26.8 (−33.3 - −18.6)^{2}	−33.3 (−55.6 - −27.5)
	Figure 8	−12.5 (−22.2 - 28.6)	−33.3 (−50.0 - −11.1)^{A}	−14.3 (−33.3 - 0.0)^{A}	−11.8 (−28.6 - 0.0)	−11.1 (−22.2 - −10.6)
	Figure 9	0.0 (−10.0 - 11.1)	−25.0 (-35.4 - −11.1)^{1}	−17.1 (−25.0 - −7.5)^{A}	0.0 (−14.3 - 0.0)	−10.0 (−15.6 - 0.0)
Female dental professionals	Figure 2	−37.5 (−60.0 - −28.6)	−50.0 (−75.0 - −38.8)^{B}	−50.0 (−55.6 - −40.0)^{B}	−37.5 (−50.0 - −20.0)^{B}	−40.0 (−50.0 - −28.9)
	Figure 3	−40.0 (−60.0 - −28.6)	−47.2 (−76.2 - −30.0)^{B}	−50.0 (−55.6 - −40.0)^{B}	−40.0 (−50.0 - −22.2)^{B}	−41.4 (−50.0 - −22.5)
	Figure 4	−33.3 (−42.9 - −25.0)^{B}	−38.8 (−55.6 - −20.6)^{B}	−37.5 (−44.4 - −28.6)^{B}	−30.0 (−50.0 - −12.5)^{B}	−30.0 (−48.6 - −2.5)
	Figure 5	−22.2 (−33.3 - 0.0)^{B}	−25.0 (−48.6 - −11.5)^{B}	−33.3 (−37.5 - −24.3)^{B,a}	−25.0 (−40.0 - −11.1)^{B}	−29.3 (−47.5 - −2.5)
	Figure 6	−42.9 (−66.7 - −28.6)	−57.1 (−77.1 - −40.0)^{B}	−50.0 (−55.6 - −37.5)^{B}	−33.3 (−57.1 - −20.0)^{B}	−40.0 (−50.0 - −22.5)^{B}
	Figure 7	−50.0 (−66.7 - −28.6)	−56.3 (−77.1 - −38.1)^{B}	−50.0 (−63.5 - −39.4)^{B}	−37.5 (−57.1 - −20.0)^{B}	−43.7 (−50.0 - −28.6)
	Figure 8	−28.6 (−40.0 - −10.0)	−30.0 (−50.0 - 0.0)	−22.2 (−40.0 - −11.9)^{B}	−11.1 (−28.6 - 11.1)	−11.3 (−28.8 - 10.7)
	Figure 9	−11.1 (−33.3 - 0.0)	−12.5 (−28.8 - 0.0)	−11.1 (−22.2 - −7.5)^{B}	0.0 (−22.2 - 0.0)	0.0 (−13.8 - 14.3)
Male laypeople	Figure 2	−17.1 (−28.6 - 0.0)	−20.0 (−33.3 - −11.1)^{A}	−12.5 (−25.9 - −10.0)^{A,b}	−12.5 (−25.0 - 0.0)	−12.5 (−25.0 - 0.0)^{A}
	Figure 3	−22.2 (−37.5 - −10.6)^{A}	−22.2 (−33.3 - −12.2)^{A}	−13.4 (−22.9 - −11.1)^{A,b}	−11.1 (−25.0 - 0.0)	−12.5 (−22.2 - 0.0)^{A}
	Figure 4	−5.0 (−16.1 - 0.0)	0.0 (−22.2 - 0.0)^{A}	0.0 (0.0 - 28.6)^{A,b,2}	0.0 (−20.0 - 0.0)	0.0 (−10.0 - 0.0)^{A}
	Figure 5	0.0 (−24.3 - 16.7)	0.0 (−22.2 - 12.5)^{A}	0.0 (−11.5 - 14.3)^{A}	0.0 (−11.1 - 0.0)^{A}	0.0 (−11.1 - 12.5)
	Figure 6	−20.0 (−41.5 - 0.0)	−23.6 (−44.4 - −7.5)^{A}	−23.6 (−30.0 - −14.3)^{A}	−11.1 (−37.5 - 0.0)	−12.5 (−25.0 - 0.0)^{A}
	Figure 7	−26.8 (−48.2 - −10.6)	−29.3 (−44.4 - −13.8)^{A}	−22.2 (−30.8 - −12.2)^{A}	−16.7 (−33.3 - 0.0)	−12.5 (−33.3 - 0.0)
	Figure 8	0.0 (−14.3 - 14.3)	0.0 (−11.1 - 2.8)^{A}	0.0 (−2.5 - 21.3)^{A}	0.0 (−12.5 - 0.0)	0.0 (0.0 - 11.1)
	Figure 9	−5.0 (−14.3 - 9.4)	0.0 (−20.6 - 2.8)	12.5 (−2.5 - 14.3)^{A}	0.0 (−12.5 - 11.1)	0.0 (0.0 - 12.5)
Female laypeople	Figure 2	−27.5 (−51.4 - −11.1)	−21.1 (−33.3 - −12.5)^{B}	−25.0 (−40.0 - −12.5)^{B,b}	−20.0 (−35.4 - 0.0)^{B}	−22.2 (−33.3 - −12.5)
	Figure 3	−30.0 (−55.6 - −12.2)	−30.0 (−40.0 - −12.5)^{B}	−28.6 (−41.4 - −20.0)^{B,b}	−25.0 (−33.3 - 0.0)^{B}	−15.5 (−35.0 - −11.1)
	Figure 4	0.0 (−22.1 - 0.0)^{B}	−5.6 (−29.6 - 9.4)^{B}	−10.0 (−22.2 - 0.0)^{B,b}	0.0 (−16.7 - 12.5)^{B}	−5.6 (−25.0 - 0.0)
	Figure 5	0.0 (−11.5 - 12.5)^{B}	0.0 (−28.8 - 0.0)^{B}	−11.1 (−26.8 - 0.0)^{B}	0.0 (−17.1 - 18.8)^{B}	−5.0 (−13.5 - 0.0)
	Figure 6	−25.4 (−51.4 - −8.3)	−26.8 (−47.5 - 0.0)^{B}	−28.6 (−40.0 - −14.3)^{B}	−12.5 (−30.0 - 0.0)^{B}	−20.0 (−25.9 - −11.1)^{B}
	Figure 7	−29.3 (−47.2 - −8.3)	−25.0 (−42.1 - 0.0)^{B}	−25.0 (−40.0 - −15.5)^{B}	−16.7 (−27.5 - 0.0)^{B}	−25.0 (−33.3 - −11.1)
	Figure 8	0.0 (−30.8 - 12.5)	−10.0 (−28.6 - 0.0)	0.0 (−12.5 - 11.8)^{B}	0.0 (−15.5 - 25.0)	0.0 (−11.1 - 11.5)
	Figure 9	0.0 (−11.1 - 13.5)	0.0 (−13.5 - 9.4)	0.0 (−10.6 - 11.8)^{B}	0.0 (−12.5 - 17.1)	0.0 (−20.6 - 11.1)

Descriptive statistics; The median (25^{th}-75^{th}) are shown as percentages. [1]When the gender and profession groups were held constant, the difference was statistically significant compare to 20-25 age group ($p<0.00156$). [2]When the gender and profession groups were held constant, the difference was statistically significant compare to 26-35 age group ($p<0.00156$). [A]When the age group was held constant, the difference between dental professionals and laypeople group was statistically significant in male groups ($p<0.000625$). [B]When the age group was held constant, the difference between dental professionals and laypeople group was statistically significant in female groups ($p<0.000625$). [a]When the age group was held constant, the difference between male and female within dental professionals was statistically significant ($p<0.000625$). [b]When the age group was held constant, the difference between male and female within laypeople was statistically significant ($p<0.000625$).

aged 56-65, the lateral tooth form was shown to be significantly more attractive than the canine itself (Table 2). Consistent with this result, Rayner et al.[29] showed that dental professionals and laypeople found smiles significantly less attractive when canine teeth were substituted without reshaping as lateral incisors.

This study also examined the effect of two different gingival margin levels on esthetic perception. The results showed that the gingival margin level did not affect the esthetic perception of either the laypeople group or the dental professional group (Table 2). This is in agreement with the findings of Kokich et al.[22] in which, by displacing 2 mm, neither dentists or non-professionals perceived the smile as unattractive. Thierens et al.[30] found that the gingival margin height of the substituted canine was ranked as the least attractive when it was most apical. The difference between the findings of Thierens et al.[30] and those of the present study might be due to the discrepancy in gingival margin levels since the difference between the original canine gingival margin and the original lateral gingival margin was evaluated without excessive recession in the current study.

Creating dental symmetry and obtaining a good esthetic result might be more difficult when only one lateral incisor is missing than when both are missing. Dental differences in a smile are viewed as less esthetic when they are asymmetric, according to answers gained from

both dental professionals and laypeople.[22,31] However, in the current study, regardless of whether the gingival margin level and tooth form modifications were applied unilaterally or bilaterally, participants showed similar levels of esthetic appreciation (Table 2). In accordance with the findings of this study, Rayner et al.[29] found no difference in unilateral or bilateral changes in their study, in which they determined the effect of canine characteristics and symmetry on perceived smile attractiveness when maxillary canines were used instead of missing lateral incisors.

The participants were asked to rank the photographs to evaluate the attractiveness of a smile because photographs are considered a proper and well-founded implement in evaluating the esthetic perception of the smile.[32] A frontal view photograph of a patient was used, and all maxillary teeth were altered by using Photoshop image editing software program that has been promoted for many years due to its advanced functionality.[22] In the methodology of this study, the authors pursued a method to make the images as imperceptible as possible with the aim of giving participants a natural esthetic smile visual sensation.

NRS is a numerically segmented variant of the visual analog scale (VAS). This scale is typically rated from 0 to 10 and includes user directions that help respondents to categorize the results using numbers.[33] In comparison to the VAS, the NRS can be used verbally with simpler ratings.[34] NRS is simple to understand[35] and adapt, and it allows for the simple and rapid assessment of subjective phenomena, such as esthetics.[36] Additionally, NRS requires the evaluator to provide less information to the respondent, reduces the time needed to obtain a response, and requires no equipment or motor skills.[35] Therefore, NRS was preferred for use in this study.

Study Limitations

The limitations of this study are that it only focused on criteria such as age, gender, and dental education; however, participant factors such as cultural background, socioeconomic status, and educational level, which may affect the interpretation of dental esthetics, were not balanced among the groups. A future study could investigate how participants' educational level and culture affect esthetic perception. Furthermore, the degree of alteration of the photographs could also increase or decrease the actual effects for each esthetic parameter. Another limitation is that the color and size of the photographs were not held constant since the survey was conducted over the internet. If the photographs were printed, different results might have been obtained. Another limitation of the current study was that it was not divided into further different groups, such as dentists and dental students.

CONCLUSION

It is unclear whether there is a relationship between gender and esthetic smile perception. In general, dental professionals were more critical than laypeople. In the male groups, younger males were more critical in their evaluations; however, in female groups, the assessments were not affected by age. Camouflaging the canine to mimic the appearance of a lateral incisor was appreciated more than the canine itself, while gingival level and symmetry did not make a difference. In this regard, clinicians should select treatment based on the patient's preferences.

MAIN POINTS

- Gender has to be considered during the decision-making process for treatment.
- Dental professionals and laypeople may have different perspectives on esthetics.
- In all evaluations, the reshaped canine as a lateral incisor is more appreciated than the unrestored form.
- Treatment should be chosen by the clinician based on the patient's preferences.

ETHICS

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (approval number: 94603339/050.01.08.01-04; project number: D-KA20/39, date: 08.12.2020).

Informed Consent: She provided informed consent for the use of her images in the survey and publication of this manuscript.

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Authorship Contributions

Concept: T.U., C.Ö., Ö.O., Design: T.U., C.Ö., Ö.O., Supervision: Ö.O., Fundings: T.U., C.Ö., Materials: T.U., C.Ö., Data Collection and/or Processing: T.U., C.Ö., Analysis and/or Interpretation: T.U., C.Ö., Ö.O., Literature Search: T.U., C.Ö., Writing: T.U., C.Ö., Critical Review: Ö.O.

DISCLOSURES

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

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RESEARCH ARTICLE

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Fibromyalgia Syndrome in Patients with Type 2 Diabetes Mellitus

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Abstract

BACKGROUND/AIMS: This study aimed to assess the frequency of fibromyalgia syndrome (FMS) in patients with type 2 diabetes mellitus (DM). Additionally, we aimed to evaluate the association of pain severity with glycemic control of DM.

MATERIALS AND METHODS: Patients with type 2 DM who were being followed up in an endocrinology clinic were included in this study. FMS was diagnosed according to the 2010 criteria set by the American College of Rheumatology. The patients' pain during the morning and sleep was evaluated by the Visual Analog Scale (VAS). Fasting blood glucose and hemoglobin A1c (HbA1c) levels were measured to assess the glycemic control of DM. Their quality of life was assessed with the Health Assessment Questionnaire (HAQ).

RESULTS: Ninety-four patients (62 female, 32 male; mean age of 56.5±10.1 years) with type 2 DM and 40 healthy controls (26 female, 14 male; mean age of 52.3±10.1 years) were enrolled in this study. FMS was diagnosed in 19.1% of the diabetic patients and 7.5% of the control group ($p=0.120$). No significant difference was observed between the HbA1c levels of the type 2 DM patients with or without FMS ($p=0.814$). There was a weak negative correlation between VAS day and night scores and HbA1c levels in the diabetic patients ($r=-0.20$, $p<0.01$; $r=-0.27$, $p<0.01$, respectively). HAQ scores were higher in the diabetic patients with FMS when compared with those patients without FMS ($p<0.01$).

CONCLUSION: FMS frequency (using 2010 ACR criteria) was higher in those patients with type 2 DM compared to the healthy controls. Furthermore, good metabolic control of DM decreased daily pain among the diabetic patients and increase their quality of life.

Keywords: Fibromyalgia, diabetes mellitus, pain, prevalence

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic condition with widespread pain. Other symptoms include fatigue, sleeping disorders, memory problems, altered sensory perceptions, bowel or bladder problems, and depression.[1,2] FMS has a prevalence of 0.2-6.6% in the general population, 2.4-6.8% in females, 0.5-1.6% in males, and 0.6-15% in special populations (healthcare workers, medical students, low socioeconomic levels, serious train crash survivors, Caucasians and Turks, the elderly, textile workers and primary care center users).[3] FMS and its associated medical comorbidities can significantly increase society's economic burden and result in work loss due to temporary or permanent disability.[4-6] FMS prevalence is found to be higher in specific populations such as inflammatory bowel disease, chronic hepatitis C, hyperprolactinemia and hemodialysis patients and diabetes mellitus.[7] Diabetes mellitus (DM) type 2 is also a chronic disease, mainly characterized by sensorial abnormalities which can mimic the

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symptoms of FMS.[8] The prevalence of fibromyalgia has been shown to be higher in type 2 diabetic patients than in the healthy population in several previous studies.[8-10] Previous studies have used the ACR 1990 diagnostic criteria (88.4% sensitivity and 81.1% specificity)[11] and found a wide range of FMS prevalence rates in type 2 DM.[8-12] According to one study, the 2010 criteria were found to be three times more diagnostic than the 1990 ACR criteria.[13,14] As far as we are aware, there was no consideration of the FMS's health effects in the diabetic population in the previous studies. Therefore, we performed this study to assess FMS frequency in patients with type 2 DM, using the ACR 2010 criteria set. The secondary endpoint was to evaluate the association of pain severity in FMS with the glycemic control of DM and to evaluate health-related quality of life in these patient groups.

MATERIALS AND METHODS

Patients and Study Design

This study was designed as a cross-sectional case-controlled study conducted between January, 2016 and January, 2019. Patients with type 2 DM who were being followed up in the endocrinology clinic were enrolled. Diabetic patients diagnosed more than six months previously, both those on oral anti-diabetic and insulin treatments, were included in this study. Those patients with anemia, hyperthyroidism, hypothyroidism, malignancy, pregnancy, pre-existing inflammatory rheumatologic diseases, abnormal neurological findings (such as allodynia, hyperalgesia, altered deep tendon reflexes), or the presence of diabetic wounds were excluded. Additionally, any patients on analgesics, anti-convulsants, or antidepressant medications were excluded since these could alter the degree of pain. Healthy volunteers from the hospital staff were recruited into this study as controls.

Data Collection

After the patients' history was taken, a single researcher made physical examinations. Complete blood count, blood biochemistry, erythrocyte sedimentation rate, C-reactive protein, urinalysis, rheumatoid factor, and thyroid-stimulating hormone were studied for differential diagnosis. The patients' glycated hemoglobin A1c (HbA1c) levels measured on admission or within the previous two months were accepted as valid. Their current pain severity was investigated, and all patients and control group members filled out a questionnaire measuring their health-related quality of life. Written informed consent was obtained from all subjects. Ethical approval was taken from Çukurova University's Faculty of Medicine Local Ethical Committee (protocol number: 46, date: 02.10.2015).

Outcome Measures

The patients' pain during the morning and night was evaluated by a 10 cm linear Visual analog scale (VAS). Respondents mark the location on a 10 cm line corresponding to their current degree of pain.

Fasting blood glucose and HbA1c levels were measured to assess the disease control of DM. HbA1c levels were measured with high-performance liquid chromatography. Fasting blood glucose levels <100 mg/dL and HbA1c levels <6.5% were accepted as good glycemic control (according to the EASD criterion).[15]

The quality of life was assessed with the Health Assessment Questionnaire (HAQ). Each question is scored between 0-3, and the total scores can range from 0 to 60; higher scores indicate worse function and more significant disability.

Statistical Analysis

For statistical analysis, the SPSS 22 program was used. The analysis was performed using non-parametric tests. Student's t-test, Mann-Whitney U, chi-square, and Fisher's exact test were used for comparisons where appropriate. For correlation analysis, Pearson's correlation analysis was used. A value of p less than 0.05 was accepted as statistically significant.

RESULTS

Ninety-four patients (62 female, 32 male) with type 2 DM and 40 healthy controls (26 female, 14 male) were included in this study. The mean age of the diabetic patients and the healthy controls were statistically similar (56.5±10.1 years vs. 52.3±10.1 years; p=0.458). The mean age of the patients with and without FMS within the diabetic group were statistically similar (55.0±7.0) years vs. 55.3±10.8 years; p=0.907). The demographic and clinical characteristics of the subjects are given in Table 1.

Table 1. Sociodemographic features and laboratory parameters of the study patients

Variables	Type 2 DM (n=94)	FMS (+) (n=18)	FMS (-) (n=76)	Control (n=40)
Age (mean ± SD), years	56.56±10.14	55.04±7.09	55.33±10.81	52.30±10.15
Gender (female) n (%)*	62 (65.9)	15 (83.3)	47 (61.8)	26 (65)
Duration of disease (months, mean ± SD)	94.91±70.90	72.66±67.40	65.53±74.84	-
BMI	29.36±4.40	24.31±4.25	28.8±4.31	25.08±4.67
Current smoker, (%)	13.5	11.1	14.4	15.0
ESR	15.05±10.51	13.4±11.98	9.97±11.0	-
CRP	0.85±3.23	0.47±0.37	0.62±2.96	-
Fasting glucose	137.66±44.54	141.00±48.89	136.89±43.80	-
HbA1c	7.30±1.57	7.22±1.28	7.32±1.64	-
VAS morning*#	3.00±2.94	5.19±3.09	2.03±2.46	1.42±2.07
VAS night*#	2.52±2.70	4.80±3.17	1.64±2.08	1.25±1.87
HAQ score**#	1.48±1.94	4.21±2.01	1.23±1.80	0.65±1.25

#p<0.05, ##p<0.001 (patients with type 2 DM vs. control) *p<0.05, **p<0.001 (patients with FM vs. patients without).
DM: diabetes mellitus, FMS: fibromyalgia syndrome, SD: standard deviation, BMI: body mass index, ESR: erythrocyte sedimentation, CRP: C-reactive protein, HbA1c: hemoglobin A1c, VAS: visual analogue scale, HAQ: Health Assessment Questionnaire.

The prevalence of FMS was statistically similar in both the diabetic group and the control group (19.1% vs. 7.5%, p=0.120). The fasting blood glucose levels were statistically similar in those diabetic patients with or without FMS (141.00±48.89 mg/dL vs. 136.89±43.80 mg/dL; p=0.734).

HbA1c levels were statistically similar in the diabetic patients with or without FMS (7.22±1.28% vs. 7.32±1.64%; p=0.814). The duration of diabetes was similar in both patient groups with or without FMS (72.66±67.40 days vs. 65.53±74.84 days; p=0.709). The mean VAS morning scores were significantly higher in the diabetic patients than in the healthy controls (3.00±2.94 vs. 1.42±2.07; p=0.003). The mean VAS night scores were significantly higher in the diabetic patients than in the healthy controls (2.52±2.70 vs. 1.25±1.87; p=0.008).

There were weak negative correlations between VAS morning and VAS night scores with the fasting glucose levels in the diabetic patients (r=-0.24, p<0.01; r=-0.27, p<0.01, respectively). There were weak correlations between VAS morning and night scores with the HbA1c levels (r=-0.20, p<0.01; r=-0.27, p<0.01, respectively). The results of correlation analysis between the fasting glucose and HbA1c levels with other variables are shown in Table 2.

HAQ scores were higher, indicating worse quality of life in the diabetic subjects compared to the healthy controls (p=0.013). HAQ scores were statistically significantly higher in the diabetic patients with FMS than the patients without FMS (p<0.01). HAQ scores were higher in the control group's FMS patients compared to those subjects without FMS (p<0.001) (Table 1).

DISCUSSION

The prevalence of FMS in the general population varies between 0.2% and 6.6%.[3] In Turkey, the incidence is believed to be around 100,000 and gradually increasing.[16] In the present study, we have found a 19.1% frequency of FMS in diabetic patients according to the ACR 2010 diagnostic criteria. There are several studies investigating the prevalence of FMS in diabetic patients. The FMS prevalence in diabetic patients was found to be 9% in the study of Patucchi et al.[9] and 23.3% in the study of Wolak et al.[10] In the studies of Yanmaz et al.[8] and Tishler et al.[12] using the 1990 ACR criteria for diagnosis, FMS prevalence in diabetic patients was 18% and 17%, respectively. According to data from the clinical database of Clalit Health Services of Israel,[17] in which they evaluated the frequency of DM in FMS patients, the prevalence of DM was found to be 19.8% among 14,296 FMS patients, which was higher than the non-FMS controls.

Table 2. Correlation analysis of pain and health quality

	Fasting glucose (r, p)	HbA1c (r, p)
Age	-0.001, 0.990	-0.936, 0.229
BMI	0.148, 0.145	0.507, 0.663
Disease duration	0.269, 0.010	-0.739, 0.471
Smoking duration	0.054, 0.615	0.189, 0.879
ESR	0.057, 0.594	-0.852, 0.374
VAS morning	0.244, <0.010	0.200, <0.010
VAS night	0.270, <0.010	0.270, <0.010
VAS global	0.270, <0.010	0.224, 0.023
HAQ score	0.063, 0.558	-0.629, 0.567

BMI: body mass index, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, HAQ: Health Assessment Questionnaire, HbA1c: hemoglobin A1c.

The ACR 1990 diagnostic criteria were used to diagnose FMS in the studies mentioned above, which do not include the symptoms of FMS apart from pain.[11] The 2010 diagnostic criteria set for FMS includes both pain and the other somatic symptoms of FMS such as fatigue, sleep disturbances, stiffness, and cognitive impairment; therefore, these updated criteria view fibromyalgia as a systemic symptom-based disease, rather than a peripheral musculoskeletal disease with the pathology centered on the tender points. The ACR 2010 criteria correctly classify FMS as 88.1%[14] but include systemic symptoms, which may be an advantage for usage in the diabetic population where chronic painful conditions could overlap.[18,19] In the study of Yanmaz et al.[8], there were no healthy age and sex-matched control groups. Instead, they used rheumatoid arthritis patients as their control group, with these patients having a higher prevalence of FMS than the healthy population. In another study conducted by Tishler et al.[12], the FMS prevalence was higher in the diabetic population than in the healthy controls. In our study, the frequency of FMS in our diabetic patients was higher than in the control group, which corroborates the former studies' data. However, the difference did not reach a statistically significant level. There are some methodological differences between our study and the former studies. Our study solely included type 2 diabetic patients and used the ACR 2010 criteria for FMS diagnosis; therefore, we could not make an exact comparison with the previous studies.

We found no differences between the FMS positive and negative diabetic groups regarding their glycemic control, but there was a weak correlation between their pain levels and fasting glucose and HbA1c levels. Similar to our study, Yanmaz et al.[8] found no difference in fasting glucose and HbA1c levels between diabetic patients with or without FMS. However, contrary to this, Tishler et al.[12] found higher HbA1c levels in diabetic patients with FMS, and they also reported a positive correlation between the number of tender joints and HbA1c levels. According to a study by Hoff et al.[20], chronic widespread pain is 1.6 times more likely among patients with DM than those without DM. Although they could not show a clear-cut association between chronic widespread pain, non-fasting glucose and HbA1c levels; they observed a linear trend of decreasing prevalence of chronic non-widespread MSCs with increasing HbA1c. Hence, with the results of these former studies and the present study, we cannot conclude that there is a causal association between blood glucose control and the occurrence of FMS. Diabetes is a leading cause of neuropathy in patients, and diabetic neuropathy mainly manifests as pain. One of our study's major limitations was that we could not objectively exclude neuropathic pain in the diabetic patients. In our study, we believe that pain severity measured with VAS could reflect both "neuropathic pain" and "pain caused by fibromyalgia". Therefore, it is possible that the negative correlation between pain severity and glycemic control in this study may be mainly due to neuropathic pain.

The quality of life in diabetic patients was lower than in the healthy controls. Moreover, the health quality was lower in those patients with FMS in both the diabetic and control groups than in those patients without FMS. Health quality can be affected by several variables such as pain, sleep disturbances, and also the presence of macro-vascular and microvascular complications. It is not surprising that the diabetic population had a worse health quality result when compared with the healthy controls. However, it should be emphasized that the concomitant FMS presence had significant negative consequences for

the patients' quality of life according to the results of the present study, which confirms the importance of the accurate diagnosis of this disease.

Study Limitations

There were some limitations of our study. First, we have not used sophisticated methods such as EMG, or vascular angiography to evaluate the existence of peripheral neuropathy or ischemic neuropathy in our subjects. We cannot ignore that DM affects vascular reactivity[21] and induces diabetic neuropathy.[22] However, the ACR 2010 criteria include some specific clinical findings such as sleep disturbances, depression, anxiety balance, and memory problems which may support FMS syndrome rather than vascular changes. Also, the duration of diabetes mellitus, which is one of the most important variables in causing diabetic neuropathy, was found to be similar in type 2 DM patients with or without FMS. Secondly, our sample size was small. Third, since this study was a cross-sectional study, we could not evaluate the effect of treatment modalities of diabetes on the occurrence of FMS. Our study's strong points were that we used the 2010 ACR criteria for FMS, which include both pain and other systemic symptoms, so this is thought to be a more accurate tool to diagnose FMS in the diabetic patient group. In addition, we had a healthy control group for comparison. What's more, as far as we know, this is the first study to evaluate the influence of FMS on the health quality of the diabetic population.

CONCLUSION

In conclusion, consistent with similar studies, we found a high FMS prevalence rate (19.1%) in type 2 DM patients compared to the healthy controls (7.5%). However, no correlation was observed between metabolic control and the prevalence rate of FMS. Diabetic patients may have an increased prevalence of pain due to different etiologies. An early and accurate diagnosis of FMS may increase health quality in this patient group. Further studies with larger sample sizes, including an objective test to exclude peripheral neuropathy, would provide a more accurate identification of FMS syndrome in the diabetic population.

MAIN POINTS

- The FMS rate is higher in type 2 diabetes patients.
- There is no correlation between glycemic control and the prevalence of FMS.
- The health quality is lower in both diabetic patients and healthy controls with FMS when compared with those patients without FMS.

ETHICS

Ethics Committee Approval: Ethical approval was taken from Çukurova University's Faculty of Medicine Local Ethical Committee (approval number: 46, date: 02.10.2015).

Informed Consent: Written informed consent was obtained from all subjects.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.C.B., T.S., M.S., Concept: N.C.B., G.A., M.S., Design: N.C.B., G.A., Data Collection or Processing: N.C.B., G.A., E.N., Analysis or Interpretation: N.C.B., T.S., E.N., Literature Search: N.C.B., M.S., Writing: .C.B., G.A.

DISCLOSURES

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

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CASE REPORT

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Abdominal Cocoon: A Rare Cause of Intestinal Obstruction. A Case Report

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Abstract

Abdominal cocoon, also known as sclerosing encapsulating peritonitis (SEP) is a relatively rare disease leading to small intestine obstruction. SEP leads to acute, subacute or chronic attacks of intestinal obstruction. Since it is a slow developing process, most patients have mild to severe intestinal obstruction signs and symptoms for a period of time. Although its aetiology is not clear, it is divided into primary (idiopathic) and secondary forms in which a trigger for the inflammatory process can be identified. Here, we present a patient with complete intestinal obstruction due to an abdominal cocoon.

Keywords: Intestinal obstruction, abdominal cocoon, rare cause of intestinal obstruction

INTRODUCTION

Abdominal cocoon was first described and named by Foo et al.[1] in 1978. Abdominal cocoon can be either primary (idiopathic) or secondary to an inflammatory process.[2] Primary SEP cases are mainly seen in adolescent women in tropical and subtropical areas, leading to theories that retrograde menstruation or gynaecologic infections are their causes.[1] However, there are other study results which state that the primary form of the disease can be seen at any age and in both sexes with a male to female ratio of 2:1.[3]

In the secondary form, various local or systemic factors can be identified as triggers of peritoneal inflammation. These factors may be medications (practolol, methotrexate, antiepileptic drugs), intra-abdominal infections (tuberculosis, bacterial peritonitis, cytomegalovirus, fungus, parasites), peritoneal dialysis, organ transplantations (liver, small intestine, kidney), intraperitoneal chemotherapy, foreign bodies, talcum powder, intraperitoneal iodine, asbestosis, silica, sarcoidosis, systemic lupus erythematosus, or familial mediterranean fever.[2]

CASE PRESENTATION

A 87-year-old male patient was admitted to the emergency department with abdominal pain, distension, vomiting and constipation for three days. He had a history of mild abdominal pain and distension attacks over the previous three years with spontaneous relief. He had undergone a right inguinal hernia operation 5 years ago in his medical history with no abdominal surgery, haemodialysis, primary peritonitis, tuberculosis, systemic organ disease or drug use. On physical examination, there was a mild abdominal distension with increased bowel sounds. On palpation, he had severe tenderness in the right upper and lower quadrants, but no rigidity or rebound sign. The patient's laboratory results were unremarkable except for rise in blood urea nitrogen and creatinine levels due to dehydration, with values of 130 mg/dL and 1.4 mg/dL, respectively. Plain abdominal X-ray revealed air fluid levels and dilated intestinal segments (Figure 1). Ultrasonography revealed dilated intestinal segments up to 4 cm in diameter in all quadrants of the abdomen. Abdominal computed tomography (CT) revealed diffuse dilated intestinal segments, and in the right lower quadrant, there was discontinuity of the intestinal segments, where there was a suspected

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obstruction with a conglomerate formation. The terminal ileum and the rest of the colonic segments were collapsed.

With the diagnosis of mechanical small bowel obstruction due yo unknown aetiology, the patient was hospitalized. Oral intake was stopped, intravenous fluid was started and a nasogastric tube was inserted. The nasogastric tube content was faecaloid. After 24 hours of observation, there was no clinical improvement in the patient's status. There was no regression in distension, no discharge of gas or faeces, and the nasogastric tube content was still faecaloid. The patient underwent an exploratory laparotomy on the second day of hospitalisation. During this exploration, small bowel conglomerate (abdominal cacoon) was found. The affected intestinal segment was between 200 cm from the ligament of Treitz and 30 cm proximal to the cecum. There were no other pathologic findings within the intra-abdominal cavity. The adhesions were dense and covered with pseudo capsules (Figure 2). Since this conglomerate was a compact structure, total excision was performed. After resection of the abdominal cocoon, a side to side small bowel anastomosis was performed using a linear stapler. The postoperative period was uneventful and he was discharged on the 10th postoperative day.

Written informed consent was obtained from the patient who participated in this study.

DISCUSSION

SEP is a rare cause of small bowel obstruction. Clinical presentations are non-specific; recurrent episodes of acute, subacute or chronic small bowel obstruction with abdominal distension, weight loss, nausea, vomiting, anorexia and vague abdominal pain are common in most cases.[4] Laboratory and radiologic findings are also non-specific. Therefore, the patients are usually diagnosed with a mechanical bowel obstruction. SEP diagnosis can be made perioperatively in most cases.

For preoperative diagnosis, plain abdominal X-ray, ultrasonography and/or CT scan can be used. Plain X-ray findings, which may show dilated loops of the small intestine with air-fluid levels, are not specific. Ultrasonography has been reported to facilitate the diagnosis and may reveal dilated bowel segments encased by a dense fibrous membrane.[5] Contrast-enhanced CT is the most useful imaging method for diagnosis of SEP. Small bowel loops, often tethered together in an enveloping peritoneum defined as the "cauliflower sign", is the characteristic appearance.[6] In a study on 22 patients with SEP, Gorsi et al.[7], found that the percentage of "cauliflower sign" was 64%. Despite all these imaging studies, preoperative diagnosis is still difficult.

SEP is classified as primary (idiopathic) or secondary, depending on the underlying pathology. Primary SEP can exist in three forms: type 1: partial capsulation of the small intestine; type 2: complete capsulation of the small intestine; and type 3: capsulation of the small and large intestine, ovary, liver, and stomach.[8] Although Primary SEP is idiopathic and is not associated with any certain cause, cytokines and fibroblasts likely influence the development of peritoneal fibrosis and neoangiogenesis.[9] In young girls living in tropical and subtropical regions, hypotheses including retrograde menstruation with a superimposed viral infection and retrograde peritonitis and cell-mediated immunologic tissue damage incited by gynaecological infections have been proposed.[9] However, these hypotheses do not explain the etiopathogenesis for all patients, since 75% of patients with primary SEP are men, premenstrual women or children, with a male to female ratio of 2:1.[9] Secondary SEP is more common, associated with many causes including prolonged beta blocker therapy (practolol), peritoneal dialysis, primary intra-abdominal infections, medications, organ transplantations, intraperitoneal chemotherapy, sarcoidosis, familial mediterranean fever, systemic lupus erythematosus, asbestosis, silica, foreign bodies, talcum powder and intra-abdominal iodine.[2]

SEP is a rare and usually slow progressive syndrome with recurrent episodes of small bowel obstruction signs and symptoms. Although some medical treatment modalities have been developed for those

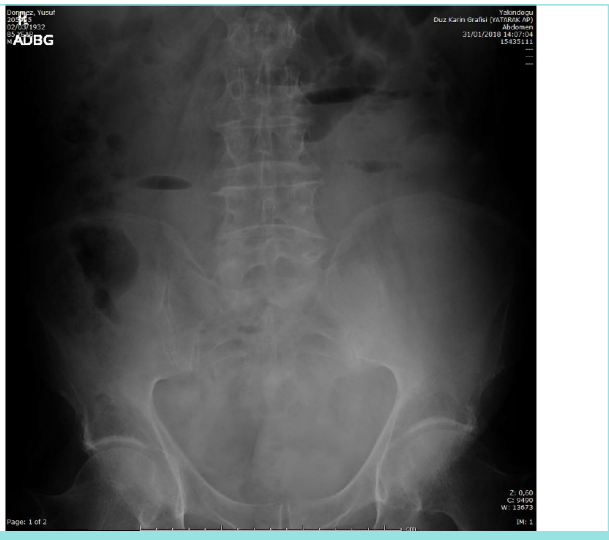

Figure 1. Air fluid levels and dilated intestinal segments on plain abdominal X-ray.

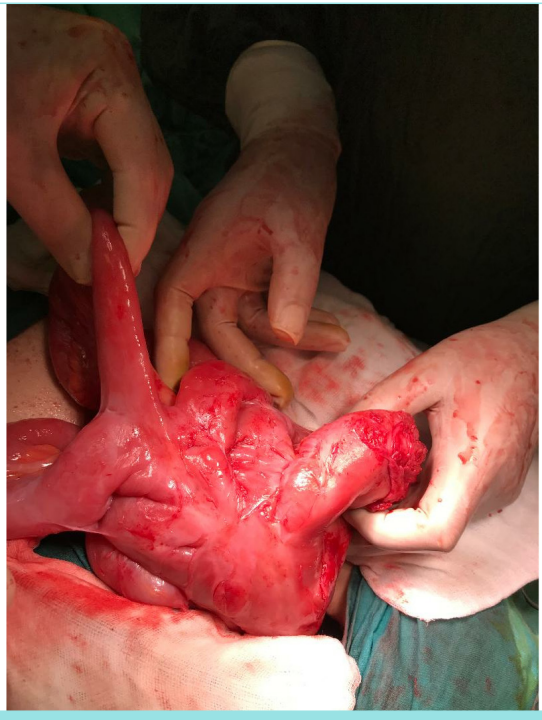

Figure 2. Small bowel conglomerate (abdominal cocoon) with dense fibrous pseudo capsule.

patients who are diagnosed before complete obstruction, especially in the Secondary SEP form, most patients need surgical intervention due to complete intestinal obstruction.[10] The preferred type of surgery is membrane excision and lysis of adhesions.[10] However, in some cases, resection of the affected segment is inevitable due to the dense adhesions. With awereness of this rare cause of intestinal obstruction, radiological imaging studies, especially CT scans, play a major role in establishing its diagnosis.

MAIN POINTS

- Abdominal cocoon is a rare and slow progressing syndrome with recurrent episodes of abdominal pain and distention.
- Laboratory and radiologic findings are usually non-specific.
- "Cauliflower sign" in CT is one of the most important imaging findings which may make preoperative diagnosis possible.
- Despite everything, definitive diagnosis can only be made perioperatively in most cases.

ETHICS

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.Ö., Design: A.Ö., Supervision: N.Ö., H.B., Materials: K.A., Data Collection and/or Processing: A.Ö., Analysis and/or Interpretation: K.A., Literature Search: A.Ö., Writing: A.Ö., Critical Review: N.Ö., H.B.

DISCLOSURES

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CASE REPORT

CYPRUS
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Coexistence of Hypertrophic Pyloric Stenosis and Long-gap Isolated Esophageal Atresia: A Case Report and Review of the Literature

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Abstract

The coexistence of hypertrophic pyloric stenosis (HPS) and esophageal atresia (EA) is a rare condition. In the literature, also, there are only a few publications written about this rare coexistent condition. In this study, an incidental HPS case, which was discovered during gastric pull-up surgery for long-gap isolated EA, is investigated. A 50-day old girl who had isolated EA applied to our clinic for gastric pull-up surgery, which was planned to replace her currently existing gastrostomy which was performed in the newborn period. During the operation, it was seen that the stomach was larger than expected because of HPS. Pyloromyotomy was carried out before gastric pull-up. Following this, the stomach was pulled upwards from the mediastinum and anastomosed with the proximal esophagus. No complication developed during or after the surgery. In cases where patients with EA come with nutrition problems, and also stricture of the anastomosis line or gastroesophageal reflux are excluded, it should be kept in mind that the reason may be HPS.

Keywords: Esophageal atresia, Infantile hypertrophic pyloric stenosis, pediatric surgery

INTRODUCTION

Esophageal atresia (EA) is a congenital pathology. It can present as an isolated defect but is often seen with additional anomalies.[1] Additional anomalies should be investigated in the pre-operative period and detailed preparation should be made for the appropriate treatment of the patient. The EA and hypertrophic pyloric stenosis (HPS) combination seems extremely rare. In the literature, there are few reports where the coexistence of these two pathologies has been described. However, in these reports, it was seen that HPS was diagnosed pre-operatively.[2-6] In this paper, we aimed to present an incidentally diagnosed HPS in a newborn during a gastric pull-up procedure due to long-gap isolated EA.

CASE PRESENTATION

A 50-day-old female patient with isolated EA was referred to our clinic for a gastric pull-up operation. When the patient was born, a nasogastric (NG) tube could not be advanced into the stomach. On the patient's chest X-ray, no gas mark was seen. The patient was diagnosed with isolated EA. After diagnosis, the patient underwent laparotomy to perform the gastrostomy procedure. No additional anomalies were detected. The patient was discharged after feeding from a gastrostomy tube and referred to a hospital for the gastric pull-up procedure.

When the patient was admitted to our clinic, the patient was being fed via the gastrostomy tube. There was no additional problem seen in the pre-operative examination. Information was given to the family about

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the procedure and its possible risks. Informed consent was obtained from the family.

At laparotomy, the stomach seemed large and more distended than expected (Figure 1). Intra-operative ultrasound was performed, pyloric muscle thickness was measured at 5.5 mm and pyloric channel length was measured at 17 mm. The pyloric muscle layer was cut parallel to the muscle lines and myotomy was performed. The stomach and distal esophagus were separated and released from the surrounding tissue. The distal esophagus was excised. The gastrostomy site was repaired. Following this, the proximal esophagus was found via neck incision. A retrosternal tunnel was created. The stomach was brought from the longitudinal tunnel. The proximal esophagus and stomach were anastomosed.

On the 4th post-operative day, feeding by NG tube was initiated. On the post-operative 8th day, contrast study was performed. No leakage or luminal stenosis were identified. Additionally, there was no abnormal finding in the pyloric passage (Figure 2). The NG tube was removed and the patient was discharged after oral intake was seen to be adequate.

DISCUSSION

Concomitant congenital anomalies are common in patients with EA. Detection of these anomalies is important in terms of pre-operative evaluation and post-operative follow-up time. Although there are not many cases presented in the literature, retrospective studies have shown that the association of EA and HPS is too high to be negligible.

EA is a life-threatening malformation in newborns and it is associated with morbidity and mortality. Pathologies which are associated with EA may affect prognosis and survival in these patients.[7]

HPS presents projectile vomiting after feeding in the first 2-12 weeks of age.[8] Progressive hypertrophy of the pyloric muscle causes obstruction of gastric emptying. Non-bilious vomiting, visible peristaltic waves in the left upper part of abdomen, palpations of the hypertrophic muscle (olive) and hypokalemic hypochloremic metabolic alkalosis are cardinal symptoms of HPS.[8] The accepted criteria for a positive United States study are a pyloric muscle thickness of more than 3 mm, and a pyloric channel length of 15 mm or more.[8]

In a retrospective study, 267 cases with EA who had been admitted to a clinic during the previous 20 years were evaluated and 24 of them had HPS.[9] The authors emphasize that this ratio is actually too high to be ignored and that pyloric stenosis should be considered in patients presenting with vomiting or non-effective feeding after EA repair.[9] Carazo Palacios et al.[10] presented two cases accompanied by these two pathologies. It was determined that these two diseases were seen together in 2 out of 66 of the patients treated in their clinic. Qvist et al.[11] found that 2 out of 74 of these two pathologies accompanied each other in their study. After repair of EA, in less than 8 weeks, patients with symptoms of gastroesophageal reflux and stricture must be investigated for absolute HPS.[11] In another case series, the authors presented cases of EA accompanied by HPS over a 5-year period. Four out of 42 patients who were admitted to the clinic during a 5-year period had HPS. Approximately 10% of these two pathologies are seen together.[6]

The diagnosis of HPS can be made between 2 and 8 weeks, since its symptoms may be delayed.[8] Repair of EA is performed in the newborn period unless it is long gap. In the early period after the repair of EA, diagnosis of HPS may be delayed due to the long duration of total parenteral nutrition and the completion of total enteral feeding.[5]

In our case, the patient's growth and development were not affected due to the undiagnosed pyloric stenosis. If the patient had not achieved the desired level of development, we might have had to have waited longer for the planned operation.

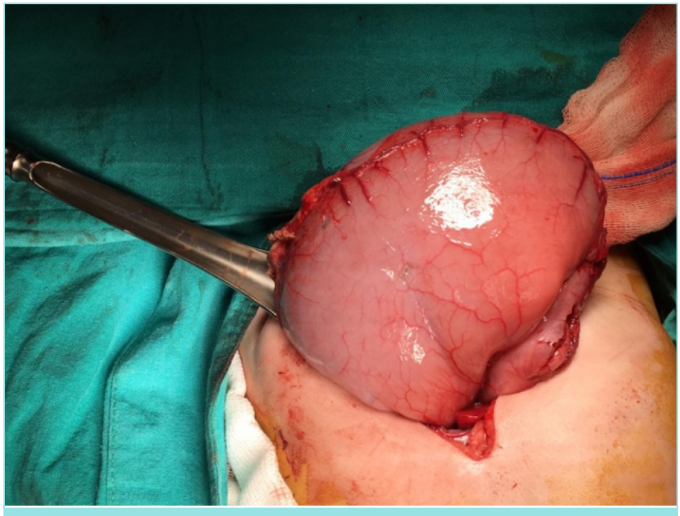

Figure 1. When laparotomy was completed, the stomach was found to be larger and more distended than expected.

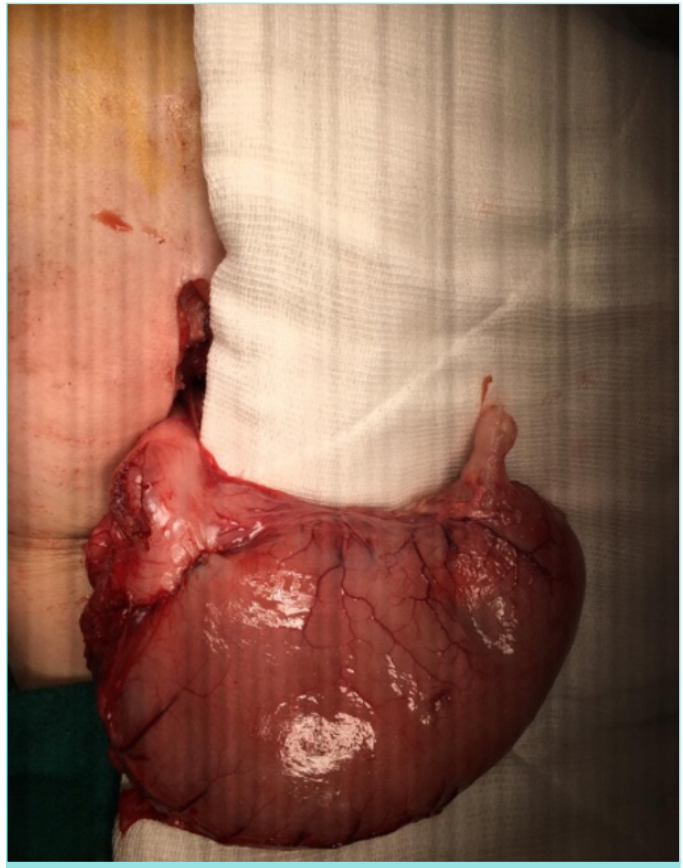

Figure 2. Hypertrophic pyloric muscle.

The stenotic stomach seemed large and wide. In this way, it was easy for the stomach to reach the neck of the patient and a tension-free anastomosis was provided. Although the large stomach was placed in the retrosternal region, there was no respiratory distress due to pressure. The patient also did not have such problems during their early post-operative period.

MAIN POINTS

- When patients present with vomiting, preliminary diagnoses are primarily due to gastroesophageal reflux and stenosis in the anastomosis line and the first symptom of HPS is vomiting after feeding.
- It should be kept in mind that these two diseases may be seen together in patients with recurrent vomiting during follow-up since the diagnosis of HPS cannot be made in the neonatal period and because symptoms are the same as reflux and stenosis, and these patients should be examined when clinical suspicion occurs.

ETHICS

Informed Consent: Informed consent was obtained from the family.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: U.A., K.B., Design: K.B., Supervision: A.Y., Materials: B.M., Literature Search: B.M., Writing: F.S., U.A., K.B., B.M., Critical Review: U.A. A.Y.

DISCLOSURES

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CASE REPORT

CYPRUS
JOURNAL OF MEDICAL SCIENCES

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Cyprus J Med Sci 2022;7(5):698-700

An Unexpected Cause of Symptomatic Bradycardia: Anti-glaucoma Eye Drops

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Abstract

Non-selective beta adrenergic blockers of which pharmaceutical form is eye drops are generally used for the treatment of glaucoma. Although applied topically, systemic side effects of these eye drops may occur. Here, a case of symptomatic bradycardia due to brinzolamide/timolol eye drops is presented. A 65-year-old woman with vertigo and dizziness was admitted to our hospital. Her electrocardiogram (ECG) revealed sinus bradycardia (heart rate 50/min). She was not using any oral negative chronotropic drugs. She was further questioned regarding her use of eye drops. She was using eye drops containing brinzolamide/timolol. She was told to stop using the eye drops. Two weeks later she was asymptomatic and her heart rate had increased to 65/min. When a patient presents with bradycardia, drug history should include topically administered drugs such as eye drops before performing further tests.

Keywords: Timolol, bradycardia, dizziness

INTRODUCTION

A topically administered fixed combination of brinzolamide and timolol is used for glaucoma treatment when intraocular pressure cannot be reduced sufficiently with monotherapy. Brinzolamide is a strong inhibitor of human carbonic anhydrase-II and inhibition of this isozyme decreases aqueous humor secretion. Timolol, on the other hand, is a non-selective beta blocker without intrinsic sympathomimetic activity which mainly decreases the formation of aqueous humor and increases outflow facility slightly. Although applied topically, these drugs may have severe systemic side effects. Here, we present a case of symptomatic bradycardia due to the use of topical brinzolamide and timolol combination.

CASE PRESENTATION

A 65-year-old woman with known ischemic heart disease and type-2 diabetes was admitted to our hospital with fatigue and dizziness. Her blood pressure was within normal limits (120/62 mmHg) but her pulse rate was 50/min. Initial physical examination did not reveal orthostatic hypotension. Further physical examination, including neurological examination, showed no pathological findings. Electrocardiogram (ECG) revealed sinus bradycardia with a heart rate 50/min (Figure 1). Transthoracic echocardiogram was normal. She was on aspirin (100 mg od), atorvastatin (40 mg od), amlodipine (5 mg od) and gliclazide (30 mg od). She had no history of taking any oral beta-blockers, non-dihydropyridine calcium channel blockers, antiarrhythmics, digitalis glycosides or parasympathomimetics. She was further questioned regarding the use of any eye drops and her answer was "yes". The name of the drug was Azarga® (Alcon Inc, Fort Worth, TX, USA) which is a topical ophthalmic solution consisting of brinzolamide 1.0% and timolol maleate 0.5%. She was using it one drop per eye twice daily. Since timolol is a beta-blocker and known to be rarely associated with symptomatic bradycardia, she was advised to stop using these eye drops and to see her ophthalmologist. Two weeks later, the patient was free of any symptoms and ECG revealed normal sinus rhythm with a heart rate of 65/min (Figure 2) after the discontinuation of the eye drops. Her symptomatic bradycardia was attributed to the use of these topical eye drops. Informed consent was obtained.

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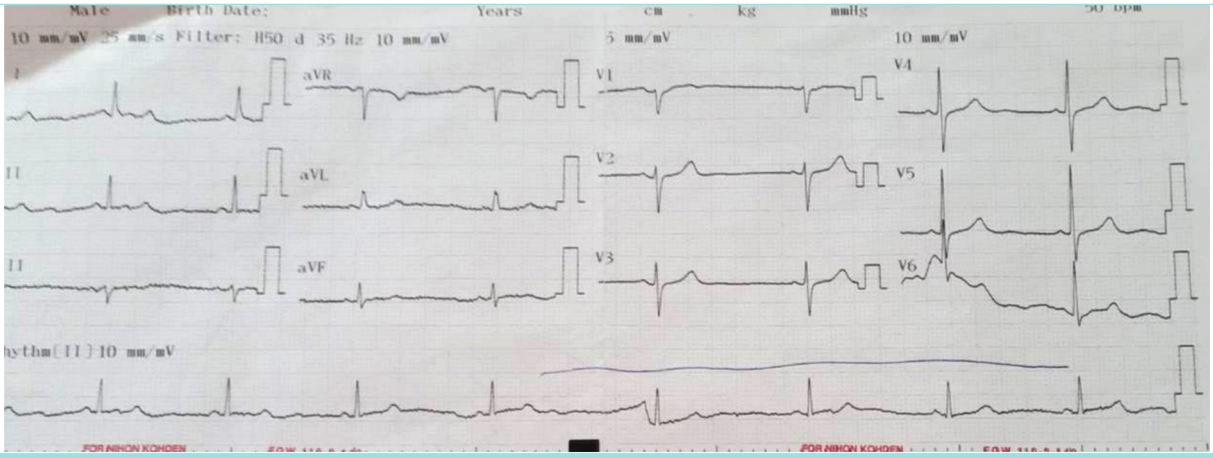

Figure 1. Initial resting ECG revealing sinus bradycardia while using eye drops.
ECG: electrocardiogram.

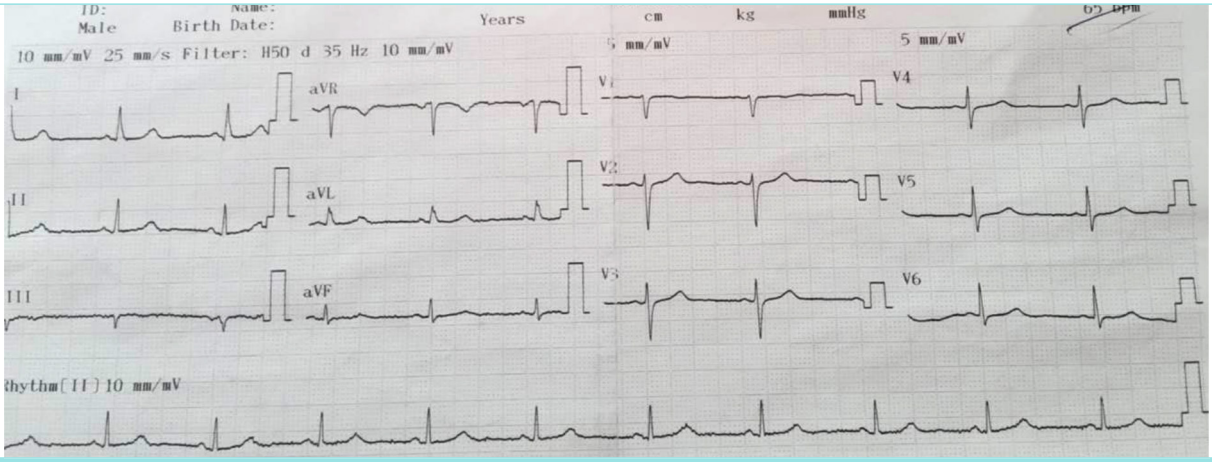

Figure 2. Resting ECG taken 2 weeks later showing normal sinus rhythm after the discontinuation of the eye drops.
ECG: electrocardiogram.

DISCUSSION

In our case, the responsible drug for the bradycardia was thought to be timolol because there is no evidence regarding systemic side effects associated with brinzolamide in the literature.[1]

Timolol is a non-selective beta-adrenergic blocking agent without intrinsic sympathomimetic activity and it has been on the market since 1978. Approximately 80% of topically applied timolol is absorbed from both conjunctival and nasal mucosa and directly enters systemic circulation, thus bypassing the pre-systemic metabolism of the liver.[2,3] This is why even when applied at small doses topically, it can cause systemic beta-adrenergic blocking effects.[2] Initial reports about timolol included only a slight decrease in heart rate.[4] On the other hand, nowadays, there are many reported adverse cardiovascular effects including arrhythmias (tachycardia and bradycardia), anginal chest pain, acute myocardial infarction, hypotension, heart failure, low blood pressure, orthostatic hypotension, heart and syncope.[4-7] A study including 14 patients treated with ophthalmic timolol showed only a minor decrease in pulse rate.[8] In another study, Dickstein et al.[9] reported similar results with a decrease in daytime mean heart rate of about 6 beats per minute (bpm) in patients with topically administered timolol eye drops. In our patient, timolol reduced the heart rate by 15 bpm which was more than expected indicating inter-individual variabilities regarding the effect of this drug. This possible exaggerated response to the drug may be associated with the age of our patient. It was shown that bradycardia associated with topical timolol may be more profound when used concurrently with oral negative chronotropic drugs. In 2006, a randomized controlled trial including 205 patients showed that in a group of glaucoma patients who were not on either topical or oral beta-blocking agents, average resting heart rate was 76 bpm, however, average resting heart rates were 70.3 bpm in those patients on topical beta-blocking agents, 64.7 bpm in patients on oral beta-blocking agents and 58 bpm in patients on both topical and oral beta-blocking agents.[10] The interaction of topical timolol with oral verapamil was also reported.[11] However, our patient had not been on any oral negative chronotropic drugs.

As shown in asthmatic patients, lacrimal occlusion may almost completely inhibit the systemic absorption of topical timolol, thus

preventing the systemic adverse events (e.g. bronchoconstriction) associated with this drug.[12]

We present this case in order to highlight the importance of careful history taking in the setting of bradycardia. Eye drops with beta-adrenergic blocking effects can have profound and sustained systemic effects, predominantly in old and fragile patients. Therefore, they should be prescribed with caution in the elderly population and in those patients with accompanying cardiovascular diseases. If such patients present with bradycardia, a thorough drug history should include topically applied medicines such as eye drops in order to avoid unnecessary further tests.

MAIN POINTS

- Eye drops, even when used as topical medicines, can have profound systemic effects.
- Beta-blocker eye drops should be prescribed with caution in older patients especially with cardiovascular co-morbidities.
- A clinician should take the patient's history carefully including all medicines with different pharmaceutical forms in order to avoid unnecessary tests.

ETHICS

Informed Consent: It was obtained.

Peer-review: Internally peer-reviewed.

DISCLOSURES

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

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CASE REPORT

CYPRUS
JOURNAL OF MEDICAL SCIENCES

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Cyprus J Med Sci 2022;7(5)701-704

Intra-Articular Tenosynovial Giant Cell Tumour of the Knee Mimicking Synovial Sarcoma: A Case Report

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Abstract

The intra-articular form of tenosynovial giant cell tumour is seen as a smooth margined soft tissue tumour which may resemble both benign and malignant pathologies. Clinical and radiologic findings are usually non-specific, and a multidisciplinary approach is important in order to make the right decision for treatment.

Keywords: Tenosynovial giant cell tumor, intraarticular form, MRI

INTRODUCTION

Tenosynovial giant cell tumour (TSGCT) is a rare benign tumour arising from joints, bursae and tendon sheaths. Intra-articular TSGCT is an uncommon form of TSGCT, involving the large joints. Lesions are usually seen as solitary painless masses. Pain and restricted movement are the most common complaints in symptomatic patients. Radiological findings are non-specific, and lesions are seen as a soft tissue masses with smooth margins in magnetic resonance imaging (MRI). Multidisciplinary team work is important before treatment as a benign lesion because of the potential of malign lesions to mimic these findings.

CASE PRESENTATION

A twenty-three-year-old male patient with anterior knee pain and restricted movement on his left knee was referred to our department. The patient claimed to have no history of trauma. Anterior knee pain increasing during extension was noted on physical examination.

The patient had been evaluated in an out-patient medical centre 3 months previously and had MRI examination without contrast administration. Tru-cut biopsy was performed through the anterolateral portal. The pathological findings were non-diagnostic, probably because the specimen was from the necrotic part of the lesion, due to insufficient evaluation of non-contrast MRI.

MRI examination was repeated at our department with a 1.5 T-system (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) with intravenous (i.v.) administration of gadolinium-based contrast agent (20 mL, 0,5 mmol/mL, gadoteric acid, Guerbet, Roissy, France). A 5x4x3 cm sized lesion filling Hoffa fat pad, extending posteriorly to the intercondylar notch anterior to anterior cruciate ligament (ACL) was detected. The lesion was isointense to muscle on T1 weighted and iso-hyperintense on Proton Density with Fat-Saturation images (Figure 1). The lesion contained a T1A hypointense and PD hyperintense focus reflecting necrosis (Figure 2). Intense enhancement was seen after i.v. contrast agent administration (Figure 3). The lesion was reported suspicious for synovial sarcoma, and histologic evaluation from the viable component of the lesion was suggested.

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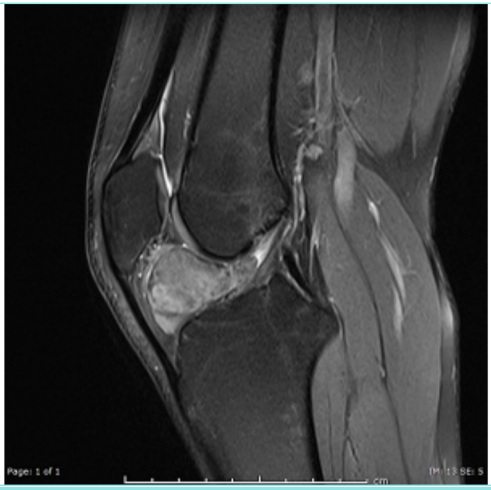

Figure 1. Sagittal PDFS image shows iso-hyperintense tumoural lesion in Hoffa fat pad, extending posteriorly to intercondylar notch anterior to anterior cruciate ligament.

PDFS: Proton density with fat-saturation.

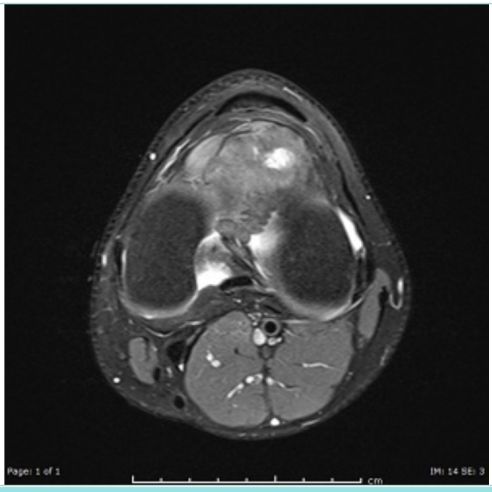

Figure 2. Axial PDFS image shows iso-hyperintense tumoural lesion containing hyperintense necrotic focus.

PDFS: Proton sensity with fat-saturation

Due to the symptoms and radiologic findings, surgery was planned. The patient was positioned supine and the ipsilateral extremity was prepped and draped. Cefazolin 1 gr i.v. was used for prophylaxis and a pneumatic tourniquet was inflated for bleeding control. A 10 cm longitudinal skin incision was made on the anterior aspect of the knee, including the biopsy tract. Skin and subcutaneous tissues were sharply dissected. Medial parapatellar incision was made to deviate the patella laterally and the knee joint was exposed. A 4x4 cm, blueish-purple, solid soft tissue tumour arising from the anterior fat pad was detected. The tumour was well-margined and limited to the infrapatellar region. Intraoperative assessment also revealed that the superior edge of the tumour protruded to the ACL without any sign of invasion. The tumour was marginally resected with the surrounding soft tissue leaving the ACL intact (Figure 4).

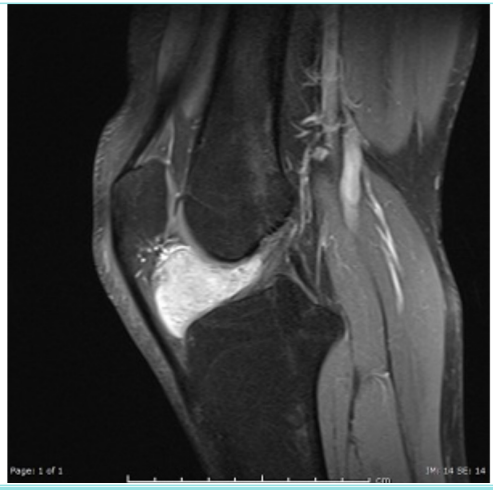

Figure 3. Coronal T1A FS post-contrast image shows intense enhancement.

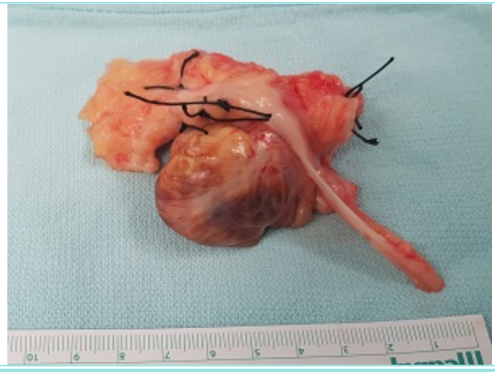

Figure 4. Specimen of resected tumoural lesion.

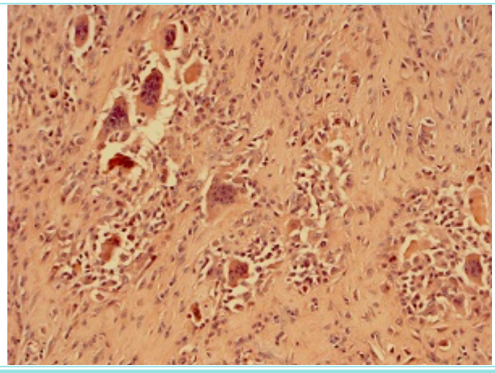

Figure 5. Microscopic appearance of the tumour with high magnification (hematoxylin & eosin, x200) shows multinucleated giant cells and mononuclear cells which have eosinophilic cytoplasm and oval shaped nuclei.

Histopathologic evaluation revealed multinucleated giant cells and mononuclear cells which had eosinophilic cytoplasm and oval shaped nuclei compatible with TSGCT (Figure 5).

The patient was pain free at his 3-month follow-up.

Written consent was taken from the patient.

DISCUSSION

In this case report, we tried to discuss the importance of cooperation between orthopaedic oncologists, radiologists and pathologists through an unusual case. Intra-articular TSCGT is a benign lesion with non-specific clinical and radiological findings. It is important to carefully evaluate the symptoms and consider the radiologic imaging protocol to gain optimal results.

Intra-articular TSGCT involves the large joints, particularly the knee.[1,2] Lesions are usually seen during the 3rd to the 5th decades.[1,3,4] While no specific gender predilection or male dominance was reported in some studies,[1,5] female predominance (1.5-2/1) was mostly stated.[3,6-8] When affected, the infrapatellar fat pad is a common region of involvement in the knee joint. The most commonly seen symptom is a painless soft-tissue mass.[3,7] Pain, swelling, fullness, restricted movement and palpable mass are other clinical manifestations of this disease.[1,3,5,9] These lesions can be pedunculated and cause acute pain because of torsion and necrosis.[10,11] Radiographic examination may show normal findings or rarely a soft tissue mass.[3] Findings by MRI are a circumscribed, sometimes pedunculated intra-articular mass, isointense to surrounding muscle on T1 weighted and iso-hyperintense on T2 weighted and PD images. A cleft-like or linear hyperintense focus related to tissue necrosis can be detected.[11] Macroscopically, lesions are seen as villous or frond-like synovial projections. Microscopically, multinucleated giant cells, macrophages, xanthoma cells and hemosiderin deposits are observed.[3]

Synovial sarcoma shows same age and gender predilection, namely the adolescent and young adult populations, with female dominancy. The infrapatellar fat pad is a common region of involvement in the knee joint.[12] In most of the cases, a common complaint is a slow growing painless mass. Larger lesions demonstrate a typical triple signal caused by haemorrhage, calcification and fibrous tissue. Periosteal reaction or extrinsic erosion at the the adjacent bone has been reported in the literature.[13] However, tumours smaller than 5 cm may demonstrate homogenous signal intensity and well-circumscribed margins, imitating benign lesions, which is very similar to our case.[14] Synovial sarcoma is macroscopically seen as a grey to yellow lesion with necrotic and haemorrhagic components. Microscopic evaluation of the most common monophasic type reveals mesenchymal spindle cells.[12]

While surgical intervention is sufficient for the treatment of intra-articular TSGCT and recurrence is rare,[5,11] wide resection and adjuvant chemo/radiotherapy are recommended for synovial sarcoma because of its high recurrence rates (30-50%) and the distant metastatic (41%) potential of this disease.[12,15] Since surgical and post-operative procedures substantially differ, highly detailed radiological and pathological assessment is important before operation planning.

Intra-articular solitary soft tissue lesion with smooth margins in MRI may reflect either benign or malignant lesions and treatment approach may differ sharply. Thus, multidisciplinary team work is important for treatment.

MAIN POINTS

- Intra-articular TSGCT is an uncommon form of TSGCT in which clinical and radiological findings are non-specific.
- Multidisciplinary team work is important before treating as a benign lesion because of the potential for malign lesions to mimic these findings.

ETHICS

Informed Consent: Written consent was taken from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Y.K., E.S., Design: Y.K., E.S., Ö.T., K.E., Supervision: Ö.T., K.E., G.M., Materials: Y.K., E.S., H.Ö., G.M., Data Collection and/or Processing: Y.K., E.S., H.Ö., Analysis and/or Interpretation: Y.K., Ö.T., K.E., Literature Search: Y.K., E.S., Writing: Y.K., Critical Review: E.S., Ö.T., K.E., H.Ö., G.M.,

DISCLOSURES

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

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