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(Dergi, yılda 4 sayı olarak Ocak, Nisan, Temmuz, Ekim aylarında yayımlanır)

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Kapak resmi: Prof. Dr. Erkmen Böke (1939-2014):

İzmir'de 1939 yılında doğdu. 1962 yılında Ankara Üniversitesi Tıp Fakültesi'ni bitirdi. 1970 yılında Almanya Heidelberg Üniversitesi'nden Genel Cerrahi uzmanlığını aldı. Türkiye'ye döndükten sonra Hacettepe Üniversitesi'nde 1970 yılında Genel Cerrahi Uzmanı, 1973 yılında da Göğüs ve Kalp-Damar Cerrahisi Uzmanlığını aldı. Aynı üniversitede 1976 yılında Doçentliğe, 1982 yılında da Profesörlüğe atandı. 1982-1988 yılları arasında Hacettepe Üniversitesi Hastaneleri Başhekimliği görevinde bulundu. Almanca ve İngilizce bilen Prof. Dr. Böke, evli ve iki çocuk babasıdır.

Resim çalışmalarına 2003 yılından beri yoğun olarak devam etmiş olan Prof. Dr. Böke, ilk iki yağlıboya kişisel resim sergisini Hacettepe Üniversitesi Ahmet Göğüş Sanat Galerisi'nde 2005 ve 2007 yıllarında, üçüncü kişisel sergisini Arsuz İskender Sayek Evi'nde "Füsun'un Çiçekleri" adıyla ve dördüncü sergisini de 2011 yılında Ankara Elele Sanat Galerisi'nde açmıştır. Prof. Dr. Erkmen Böke, yedi karma sergiye katılmıştır.

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Cover image: Prof. Dr. Erkmen Böke (1939-2014):

He was born in Izmir in 1939. He graduated from Ankara University Faculty of Medicine in 1962. In 1970, he received his General Surgery specialty from Heidelberg University, Germany. After returning to Turkey, General Surgeon at Hacettepe University in 1970, also in 1973, took/finished the Thoracic and Cardiovascular Surgery Specialty. He was appointed Associate Professor in 1976 and Professor in 1982 at the same university. Between 1982-1988, he worked as the Chief Physician of Hacettepe University Hospitals. Speaking German and English, Prof. Dr. Böke is married and has two children.

Prof. Dr. Böke opened his first two personal oil painting exhibitions at Hacettepe University Ahmet GÖĞÜŞ Art Gallery in 2005 and 2007, the third one at the Arsuz İskender Sayek House under the name "Flowers of FÜSUN" and the fourth one at the Ankara Elele Art Gallery in 2011. Prof. Dr. Erkmen Böke participated in seven group exhibitions.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Biophysics / Biyofizik

Investigation of Cholera Toxin Interaction Mechanism for Structure-Based Drug Design

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[1]Trakya University Medical Faculty, Department of Biophysics, Edirne, Turkey

Ayhan ÜNLÜ

ABSTRACT

Cholera is a disease that is developed by parasitizing the bacteria called vibrio cholera in the small intestine of people and it causes severe watery diarrhea, if it is left untreated, it can result in death. The bacteria is transmitted to the people through the digestive tract with water and nutrients, starting with vomiting and going on with severe diarrhea. A potent enterotoxin, Cholera Toxin (CT) which is secreted by vibrio cholera is largely responsible for the disease. It first emerged in India and began to spread to the world between 1827-1975. The cause of the disease, Vibrio cholerae bacteria, which has been known since ancient times with high outbreaks and high mortality rates, has less resistance to external influences and dies in 10-15 minutes at 55°C and in 1-2 minutes at boiling temperature. They are not able to resist dryness, sunlight and acids. Gastric acidity inactivates the vibrations in a short time, which protects many people from being caught in cholera. ADP-Ribosylating Toxins (ADPRT), also including cholera toxin synthesized by this bacteria, are a large and potentially fatal toxin family. They are secreted by pathogenic bacteria and inhibit the functions of human target proteins. Based on structure-based multiple sequence alignments, the ADPRT family is classified into two groups according to the Nicotinamide Adenine Dinucleotide (NAD) that binds Diphtheria Toxin (DT) and CT. DT group toxins change eukaryotic elongation factor 2 and disrupt protein synthesis in eukaryotic cells. DT, exotoxin A (ETA) and cholix toxin are among the members of this group. CT group toxins target various essential proteins in host organisms. For example, CT and temperature-varying enterotoxin target Arg on Gs-R on G protein. This leads to uncontrolled adenylate cyclase activity. Although ADPRT enzymes exhibit a variety of functions and low sequence identities, they share common structural and functional characteristics. This toxin family has the ability to catalyze NAD by using the same pathway with poly ADP-ribose polymerases. We think that being clarified as a matter of the cholera toxin structure, which is the member of this family, will play an important role in the development of many drug design studies such as being able to interfere in significant proteins structure for cancer cells and the development of various catalysis mechanisms. In this study, we investigated the three-dimensional structure of cholera toxin, which is an important member of the ADPRT family, and the interface which will interact with the other amino acids whose binding energies are higher than other amino acids which are situated in the structure (hot spot) by using theoretical and experimental methods. As a result of our theoretical and experimental studies we think that the 12 amino acid sequence of Cholera toxin, constituting the common structural region that binds to NAD in the ADP-ribosylating toxins family is the sequence of 61- STSISLRSAHLV-72.

Keywords: Cholera Toxin, ADP-ribosylating toxins, poly ADP-ribose polymerases, nicotinamide adenine dinucleotide (NAD), protein-ligand interaction

Yapı Bazlı İlaç Tasarımı İçin Kolera Toksin Etkileşim Mekanizmasının İncelenmesi

ÖZET

Kolera, vibrio kolera adı verilen bakterilerin insanların ince bağırsağında konaklamasıyla gelişen ve şiddetli sulu ishale neden olan ve tedavi edilmediğinde ölümle sonuçlanabilen bir hastalıktır. Bakteriler su ve besinlerle, sindirim yolu aracılığıyla insanlara bulaşır ve hastalık kusma ile başlayıp şiddetli ishalle devam eder. Hastalıktan büyük ölçüde sorumlu olan Kolera Toksini (CT), vibrio kolera tarafından salgılanan güçlü bir enterotoksindir. Hastalık ilk olarak Hindistan'da ortaya çıkmış ve 1827-1975 yılları arasında dünyaya yayılmaya başlamıştır. Hastalığın nedeni olan Vibrio Kolera bakterisi eski zamanlardan beri salgınlara ve yüksek ölüm oranlarına sebep olarak bilinmektedir. Bakteri dış etkenlere karşı dirençsizdir ve 55^{0}C'de 10-15 dakikada, kaynama sıcaklığında 1-2 dakikada ölür. Kuru ortamlar, güneş ışığı ve asite direnemezler. Mide asiti titreşimleri kısa sürede etkisiz hale getirir. Böylece çoğu insan koleraya yakalanmaktan korunur. CT, ADP-Ribozilleyen Toksinler (ADPRT) ailesine dahildir. Bu toksin ailesi geniş ve potansiyel olarak ölümcül toksinlerdir. Patojenik bakteriler tarafından salgılanırlar ve insan hedef proteinlerinin foksiyonlarını inhibe ederler. ADPRT ailesi, difteri toksini (DT) ve kolera toksinini (CT) bağlayan NAD'a (Nikotin Amid Dinükleotot) göre iki gruba ayrılır. DT grubu toksinler elengasyon faktörü 2 'yi değiştirir ve ökaryotik hücrelerde protein sentezini bozar. DT, ekzotoksin A (ETA) ve cholix toksin bu grubun üyeleri arasındadır. CT grubu toksinleri, konakçı organizmadaki çeşitli temel proteinleri hedefler. Örneğin CT ve sıcaklıkla değişen enterotoksin, G proteininde Gs-R üzerindeki Arg'yi hedefler. Bu, kontrolsüz adenilat siklaz aktivitesine yol açar. ADPRT enzimleri çeşitli işlevler ve düşük dizi benzerlikleri göstermelerine rağmen, ortak yapısal ve işlevsel özellikler gösterirler. Bu toksin ailesi, ADP-riboz polimerazlarla aynı yolu kullanarak NAD'ı katalize etme yeteneğine sahiptir. Bu ailenin bir üyesi olan kolera toksin yapısının aydınlatılmasının, kanser hücreleri için önemli olan protein yapılarına müdahale edilebilmesi ve çeşitli kataliz mekanizmalarının geliştirilmesi gibi birçok ilaç tasarımı çalışmasının geliştirilmesinde önemli rol oynayacağını düşünmekteyiz. Bu çalışmada, ADPRT ailesinin önemli bir üyesi olan kolera toksininin üç boyutlu yapısını ve bağlanma enerjileri, yapıda bulunan diğer aminoasitlerden yüksek olan aminoasitlerle etkileşime girecek arayüzünü, deneysel ve kuramsal yöntemler kullanarak araştırdık. Teorik ve deneysel çalışmalarımız sonucunda, ADP ribozilleyen toksinler ailesinde NAD'a bağlanan ortak yapısal bölgeyi oluşturan Kolera toksininin 12 aminoasitlik dizisinin 61- STSISLRSAHLV-72 olduğunu düşünüyoruz.

Anahtar Sözcükler: Kolera Toksini, ADP-ribozilleyen toksinler, ADP-Ribozil Polimerazlar, Nikotin adenin Dinükleotit, Protein-Ligand etkileşimi

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The Italian Filippo Pacini first identified cholera toxin (CT), produced by Vibrio Cholerae (VC), as the cause of cholera in 1854 (1), and Robert Koch rediscovered it nearly 30 years later (2). He postulated the existence of CT in 1886, claiming that the symptoms induced by Vibrio cholerae which is caused by a toxin generated by the bacterium. S. N. De in Calcutta in 1959 verified this insightful hypothesis, demonstrating that cell-free extracts from VC cultures could produce excess fluid in rabbits when injected into ligated small intestine loops (3). In the same year, NK Dutta and colleagues at the Haffkine Institute in Bombay, India, revealed that a crude protein extracted from the culture filtrate of V. cholerae causes diarrhea in newborn rabbits (4), confirming De's findings. De's discovery of the cholera toxin and its exotoxin nature laid the groundwork for present cholera study into the disease's molecular basis. Richard Finkelstein's group was able to isolate and purify the CT (5,6). Using gel filtration chromatography and membrane ultrafiltration, his team isolated the active ingredient from V. cholerae culture supernatants and named it "choleragen." SDS-polyacrylamide gel electrophoresis, which dissociates and separates noncovalently bound protein components, revealed two distinct kinds of subunits in cholera toxin. The terms "choleragen" and "choleragenoid" were distinguished. The latter was a protein with a molecular weight of about 56,000 Da that generated spontaneously from the dissociation of choleragen and was named choleragenoid. It was antigenically similar to the original toxin, however it lacked the toxin's harmful properties. The B-subunit pentamer was later X-ray crystallography at 2.5 A resolution was used to solve and improve the three-dimensional structure of hexameric AB5 CT (7). This structure is similar to that of Escherichia coli heat-labile enterotoxin, with which cholera toxin has 80 percent sequence homology. The poisonous A-subunit is found embedded in the symmetrical pentameric pore-like structure produced by five B-subunits, according to X-ray crystallographic investigations (8). Despite being generated as a single polypeptide chain, the mature A-subunit (240 aa) is eventually separated into two sections: a wedge-shaped A1 domain and an elongated A2 domain with an alpha helical structure and a tail that extends through the pore formed by the B-pentamer discovered as harmless and immunogenic. Finkelstein's team was able to crystallize choleragen and choleragenoid, then recombine them to make active toxin (9). The active principle "choleragen," which is toxic in nature and is known as A-subunit, as well as the nontoxic B-pentameric "choleragenoid," both played a role in eliciting cholera symptoms. Biochemical studies later revealed that CT's heterogeneous subunit structure consists of one A-subunit linked to five B-subunits.

The Structure of CT

Cholera toxin is a member of the AB5 bacterial toxin family (10), so named because of its unique architecture, which consists of a catalytically active A-subunit and a nontoxic pentameric B-subunit (B5) (Figure 1). CT is a heterogeneous protein make up of two types of subunits (11): a large one with an estimated molecular weight (MW) of approximately 28 kDa and several small ones with estimated MWs of 8–10 kDa each and an aggregate size of ca 56 kDa.

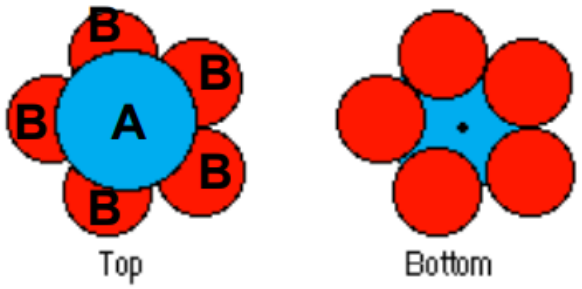


Figure 1: A and B subunit of Cholera Toxin

A-subunit has a length of 258 amino acids (aa). The signal peptide (1–18 aa), A1 chain (19–212 aa), and A2 chain (213–258 aa) are all included. The hazardous enzymatic activity is caused by the A1 chain, also known as CT alpha chain or NAD diphthamide adenosine diphosphate (ADP)-ribosyl transferase. Cholera enterotoxin gamma chain is another name for the A2 chain (12). A disulfide bridge between cysteines at locations 205 and 217 aa connects the two chains A1 and A2. Protein ADP-ribosylation domain is found in the A1 subunit. The monomer of the B-subunit is 124 amino acids long. A signal peptide (1–21 aa) and a mature B chain (22–124 aa) make up this segment. A pentameric ring is formed by the assembly of five B-subunits (13) (Figure 2).

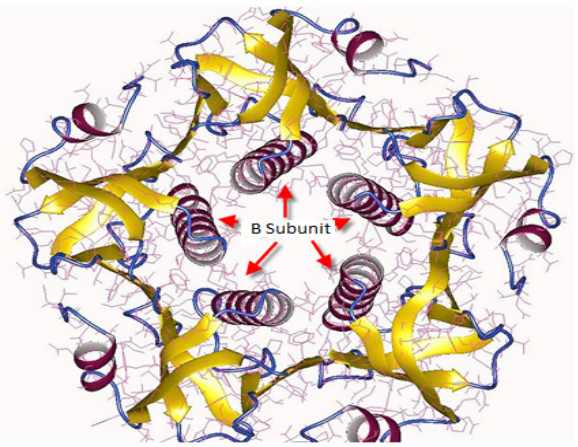


Figure 2: Secondary Structure of CT

A-subunit's secondary structure is made up of a combination of alpha-helix, beta-sheet, and random coil structural components. The alternative alpha and beta chains make up the majority of the A1 chain (19–212 aa), whereas the alpha-helical structure makes up the majority of the A2 chain. The amino acid residues are distributed among just two alpha-helices in the secondary structure of the CT B-subunit (14), with the remaining beta-strands enabling its membrane attachment feature. It consists of a single disulfide bridge between cysteines at 30 and 107 aa residues.

X-ray crystallography at 2.5 A resolution was used to solve and improve the three-dimensional structure of hexameric AB5 cholera toxin (6). This structure is similar to that of Escherichia coli heat-labile enterotoxin, with which cholera toxin has 80 percent sequence homology. The poisonous A-subunit is found embedded in the symmetrical pentameric pore-like structure produced by five B-subunits, according to X-ray crystallographic investigations. Despite being generated as a single polypeptide chain, the mature A-subunit is eventually separated into two parts: a wedge-shaped A1 domain and an elongated A2 domain with an alpha helical structure and a tail that extends through the pore formed by the B-pentamer.

At least 20 hydrogen bonds and inter-subunit salt bridges stabilize the B-pentamer, with 10 of them located in the central pore. Furthermore, hydrophobic groups bind tightly at the subunit interface, generating significant packing of subunits against one another. This gives B-subunits in the intestinal environment a lot of stability when it comes to bile, proteases, and other things. The inner surface of the ring of B-subunits is hydrophobic, and a number of positive and negative charges line the central wall.

The pentamer's monomers form a six-stranded antiparallel β-sheet with a sheet from the next subunit, giving the ring a smooth outer surface, and lengthy-helices form a helical barrel in the core. During the creation of their structure, these helices softly bend inward, lowering the effective diameter of the pore from 16 A (amino terminus) to 11 A (carboxyl terminal).

The A2 domain and the B-pentamer are involved in the non-covalent interactions between the A and B subunits. The A-A1 subunit's and A2 domains are connected by an exposed loop with a proteolytic cleavage site (after arginine 192) and a disulfide bond that spans the cleavage site. The enzymatically active A1 peptide is generated by proteolytic cleavage within the exposed loop of the A-subunit, which is responsible for hazardous action. The scaffolding that holds the A- and B-subunits together is formed by the A2 chain. The remaining four amino acids at the COOH-terminal of A2, lysine-aspartate-glutamate leucine or KDEL, emerge from the associated toxin molecule and are not involved in interactions with the pentameric B-subunit.

In this study for theoretical studies, a template file of Cholera toxin which is registered in the protein data bank with the code 2A5F was used, and also for experimental studies, lyophilized powder toxin which is known as sigma-C8052 obtained from Vibrio Cholera was used in the study.

MATERIALS AND METHODS

Molecular dynamics (MD) simulations

We were able to achieve the optimum model by combining the docking process with MD simulation to optimize the protein interface structure. Nonetheless, explicit constraint functions were not applied to retain the original docking connections during the simulation. Using the Kollman all-atom force field, the energy was initially reduced using 1000 steps of steepest descents and conjugate gradient was minimized in 2000 steps for structures. The unbounded cutoff and dielectric constant were set at 1 and 8 A, respectively, and the dielectric function was distance dependent. Energy minimization with a classical force field was used to reduce unrealistically close steric clashes and substantial deviations that emerge from perfect geometry of conformational changes of amino acid side chains following docking. The energy-minimized structure was used as the starting point for the MD simulation. All MD simulations were performed using the NAMD (Not (just) Another Molecular Dynamics program) molecular simulation tool. The interactions between CT and NAD version 2.9 were examined using molecular dynamics (MD) simulations at 300 K and pH 7.0. A parallel molecular dynamics algorithm named NAMD was created to achieve high-performance simulation of massive biomolecular systems. NAMD has a number of advantages, including the ability to run on single desktop and laptop computers, as well as the ability to expand to hundreds of processors on high-end parallel platforms and tens of processors on low-cost commodity clusters. MD simulation was utilized to identify particular interactions at the interface, compute inter-residue lengths, and other computations, and the final structure was produced.

Molecular docking

By using Autodock, the collected data of modeled structures (pdb-format) from DataBank were combined with supplemental data for cholera toxin. For genetics modeling, Lamarck's mechanism was applied, which is the notion of acquired traits being transmitted down from one generation to the next. The protein was given Kollman united atom charges (15), solvation parameters, and polar hydrogen, and Autodock employed Gastegier charges. The default distance between grid points was set at 0.375. Grid boxes' x, y, and z axes were set to 480, 260, and 280, respectively. These dimensions included all of CT's amino acid residues as well as grid sizes big enough to include all of CT's domains. The initial goal was to decode the binding domain. The step size was 0.2, and 50 simulation runs were completed. The torsion and orientation angles were both 50 degrees. 1000.0 for grid energy, 0.5 for cluster tolerance, 0.8 for crossover rate, 0.02 for mutation rate, 1 for maximum number of top individuals, and 1000 for maximum number of generations are the other adjusted data values.

Obtaining the subunits of Cholera toxin by Trypsin Partial Digestion

CT was partly digested for 60 minutes at 37 degrees Celsius in the presence of 50 mM Tris-HCl with trypsin (molar ratio 1/200), 250 mM sucrose, 7 mM MET, and 0.2 mM PMSF at pH 7.4. To inhibit the process, a 1:1 ratio of soybean meal-derived trypsin inhibitor was added, then denatured with SDS. Electrophoresis (SDS-PAGE) and chromatographic techniques were used to purify trypsin-separated fractions. Protein concentration spin columns were used to concentrate the samples (Vivaspin-10.000). ELISA was used to assess the level of ADP-ribosylation activity in the samples.

Chromatography Analysis

The study employed a HiPrep Sephacryl S-100 (16 x 60 cm) column for filtration chromatography. The column's total volume (Vc) was determined to be 120 ml, with a dead volume (V0) of 40 ml. Aprotinin (6,5 kDa), carbonic anhydrase (29 kDa), ovalbumin (43 kDa), BSA (66 kDa), and conalbumin (75 kDa) standards were used to calibrate the column, and gel-phase distribution coefficients (μ) were determined and a calibration graph was constructed based on the arrival volume. Mobility was calculated using the following formula:

$$\mu = \frac{Ve\text{-}Vo}{Vc\text{-}Vo}$$

The protein samples were divided into fragments, and the arrival volumes of these pieces were determined using the calibration graph. The samples' optical densities were evaluated at 280 nm, 0.35 mPa pressure, 0.8 ml/min velocity, and 0.5 ml after separation.

Electrophoresis Analysis

The Laemmli technique (16) was used to evaluate the samples using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). To create a 12 percent separation gel, a silicon separator was placed between the glass plates. To obtain a smooth gel surface, a 1 cm water layer was produced and allowed to polymerize for 30 minutes. After pouring the water layer on the gelatin, a 5% healing gel was applied. The comb was expected to polymerize when it was put between glass platens to form wells for loading samples. The samples were boiled for 2 minutes after being combined with a denaturing buffer at a 1: 1 ratio. Run-off buffer was added to the electrophoresis tank. During sample loading, a multi-protein standard (Fermentas Protein Ladder) with molecular weights ranging from 10 to 260 kDa was used as a molecular weight standard in a well. The current cutoff occurred when the labeling dye had reached the end of the gel. The gel was removed from the glasses and coomassie brilliant blue was used to stain them. The excess dye was then removed from the gel using a mixture of 7% acetic acid and 30% methanol. The gel, which had been dyed with protein bands, was put on 3 mm Whatman filter paper, covered with stretch film, and dried in a gel drier under vacuum for an hour at 80 °C.

Thermal Shift Assay

Heat Shift Assay is a real-time PCR assay that detects thermal denaturation of proteins in the presence of a fluorescent dye (SYPRO orange). The intensity of fluorescent light is displayed as a function of temperature, forming a sigmoidal curve characterized by a two-state transition. The Boltzmann equation was used to calculate the transition curve's turning point (Tm). A PCR equipment and a related "96 well plate" were utilized for the analysis. For each sample, the experiment was carried out three times. PARPs were applied in increasing quantities to the PARPs applied groups prior to the addition of SYPRO Orange. The fluorescence intensity was measured between 15 °C and 90 °C with an interval of 0.5 °C at 450-490 nm excitation and 560-580 nm detection throughout a 10 second time period (0.5 °C / 15 sec).

RESULT AND DISCUSSION

Although A fraction of this enterotoxin synthesized by Vibrio cholerae is a single molecule, B fraction is in the form of 5 molecules. After the B component of the toxin binds to the surface of intestinal epithelial cells, the A subsection enters the cytoplasm and decomposes there. This fraction disrupts the function of the regulatory protein that controls the activity of the enzyme adenylate cyclase in cells and makes it ineffective, so that adenylate cyclase shows continuous activity. This over-synthesized substance causes ATP to turn into cyclic AMP (cAMP) in excess. In cAMP this substance causes excess fluid and electrolyte to pass through the intestinal epithelial cells into the lumen. Since a significant part of the fluid comes from the blood, it causes the bicarbonate to come out of the blood together with the fluid and the pH of the blood to decrease, and accordingly it leads to the formation of acidosis, which initiates a process that becomes a problem for the host cells.

In our study, in order to understand the structure of CT, the crystal images of the three-dimensional structure of the toxin were displayed in the PyMol program and the regions where it interacted were analyzed (Figure 3). Our study was completed on the TR-Data Grid National Information Network, available for researchers within TUBITAK, by performing molecular dynamics calculations such as exact determination of attachment points on the CT, flexibility calculations, and various simulation studies.

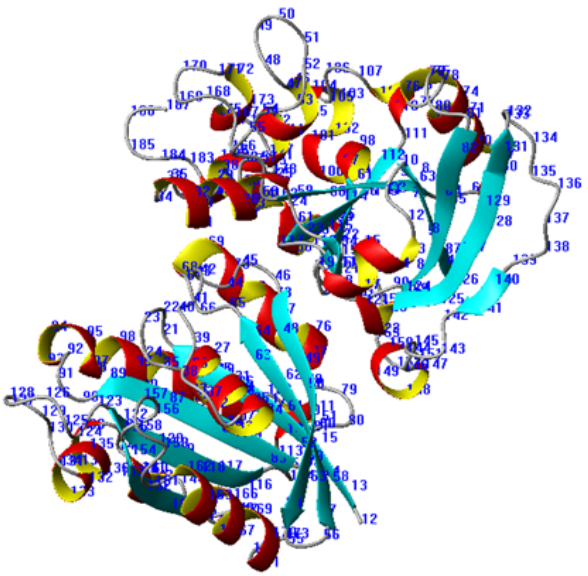


Figure 3: Secondary Structure of Cholera Toxin

The determined structure of cholera toxin was simulated with water molecules at 300°K to determine its most probable conformation (Figure 4)

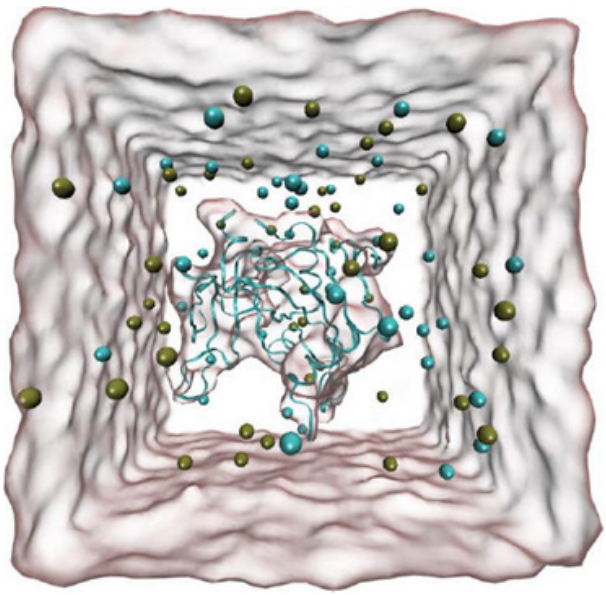


Figure 4: Cholera Toxin Simulation Study

During these processes the required regions were ordered from smallest to largest according to the calculated energies of the most likely interaction regions by subtracting similarity scores with a set of structural and geometric alignment algorithms. In the theoretical calculations, bond flexibility, bending angles, dihedral angles, interactions of amino acids with H atoms in the liquid medium where amino acids exist, Van der Waals interactions between atoms that make up amino acids, and electrostatic interactions arising from the charges of atoms were taken into account.

Cholera toxin interacted with NAD using the Docking method. As a result of interaction analysis, the 12 amino acid region (called 61- STSISLRSAHLV-72) binding NAD were detected (Figure 5), and energy calculations of the region were made (figure 6) (Table 1).

Table 1: Energy calculations of binding region of CT

	ΔG (coulomb)	ΔG (vdw)	ΔG (covalent)	ΔG bind
Cholera Toxin	-16,822	-36,678	9,169	-47,392

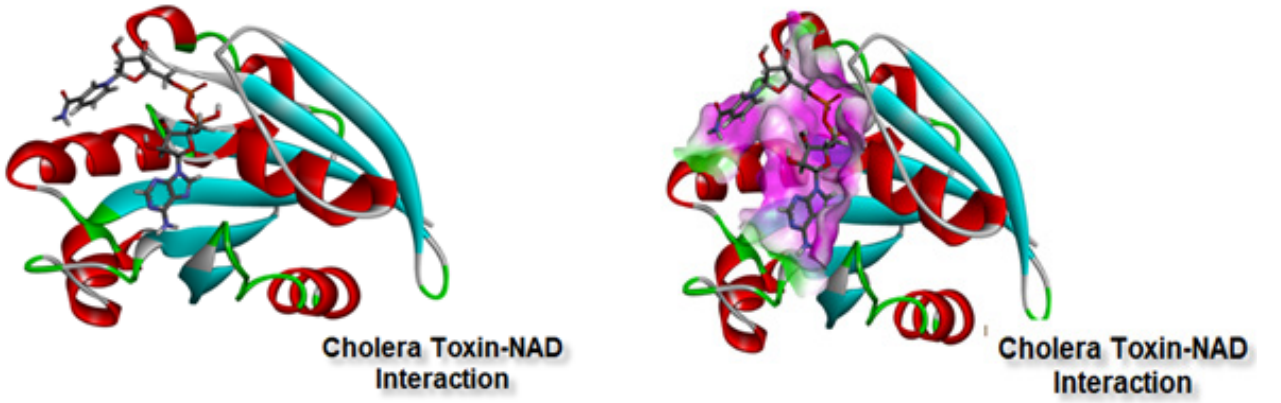


Figure 5: Interaction Area of Cholera Toxin with NAD.

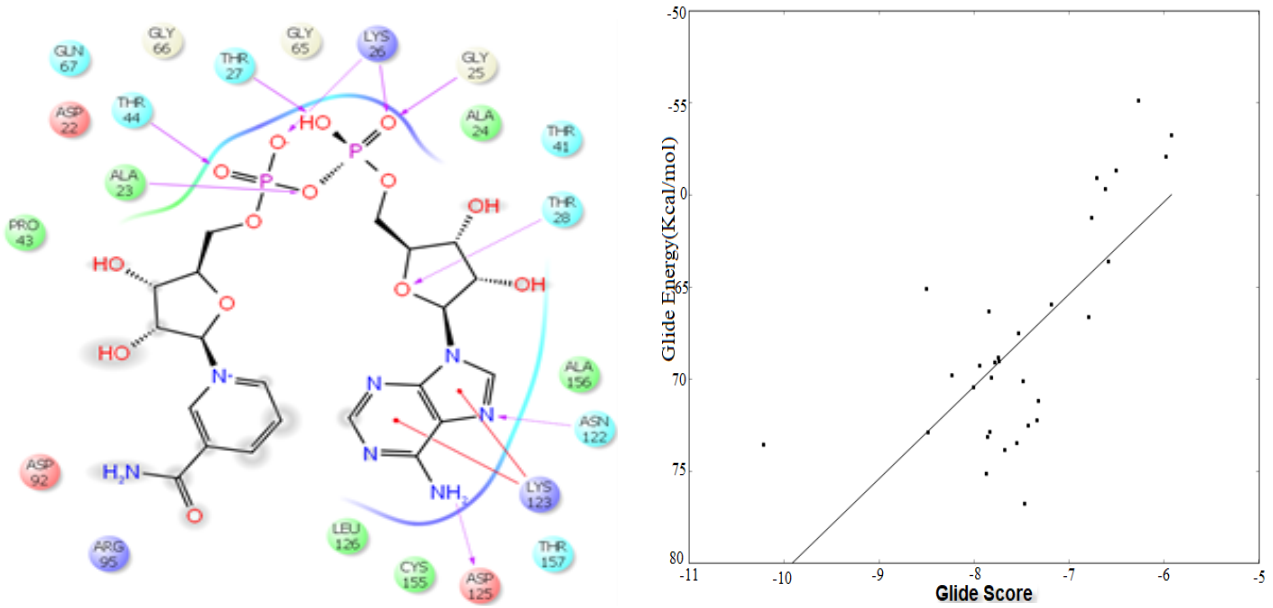


Figure 6: Interaction residue and energy calculations of Cholera Toxin with NAD.

In order to analyze binding interactions between cholera toxin and NAD+, molecular dynamics (MD) simulations and the CHARMM algorithm at 300 °K mean temperature and under pH 7 were used. Also, to find the flexibility of cholera toxin and the most probable conformation which it can be found in, the NAMD algorithm was used; and besides the studies are still ongoing down to the nanosecond range. Protein docking studies were performed using the autodock program. In the studies the calculations were made using a fixed protein docking program based on the Fast Fourier Transform (FFT) correlation approach, and they were extended to use the potentials for double logical interaction.

By adding Diphtheria Toxin (1TOX), Cholera Toxin (2A5F), loto Toxin (1GIQ), vip2 (1QS2) and Cholix Toxin (2Q6M) from ADPRT groups to our study, the structures of these extracellularly produced toxins were investigated in molecular dynamics methods. Before the studied ADPRTs are interacted with NAD in the most ideal conditions in the computer environment by using the AutoDock program, the process of preparing a series of data sets was started. In the study receptor grids were created for ADPRTs by using PDB (Protein Data Bank) files. In the next step the ligand chemical structure for NAD was prepared using the AutoDock program. The similarity (RMSD) calculations of representatives of both groups were extracted (Table 2).

Table 2: Comparative RMSD Values (Å) of ADPRT groups					
RMSD (A)	**Diphteria Toxin**	**Cholera Toxin**	**Iota toxin**	**Vip2**	**Cholix**
Diphteria Toxin	0,00	4.14	4.40	4.12	3.17
Cholera Toxin	4.14	0,00	3.93	5.45	4.50
Iota toxin	4.40	3.93	0	2.63	4.50
Vip2	4.12	5.45	2.63	0,00	3.90
Cholix	3.17	4.50	4.50	3.90	0,00

After the prepared data sets, in order to determine the interaction sites of the common motif that recognizes NAD, so that ADPRTs can catalyze NAD, the necessary docking was done to determine the binding energy required for the interaction interface of this common motif to bind to the NAD region. As a result of the docking process, the binding energies were calculated in order to determine the interaction regions with the highest probability of binding by using the Glide XP scoring technique (Table 3).

Table 3: Free Energy Binding Calculations of ADPRTs with NAD				
	ΔG (coulomb)	**ΔG (vdw)**	**ΔG (covalent)**	**Δ G bind**
Cholera Toxin	-16,822	-36,678	9,169	-47,392
Iota-Toxin	-43,382	-57,098	12,396	-62,209
VIP2	-12,039	-57,08	10,319	-65,618
Diphteria Toxin	-59,308	-50,099	-2,541	-92,407

Then, the motifs formed by the toxin groups and recognizing and catalyzing NAD were overlapped and the structural similarities were examined, and the common structural model was displayed (Figure 7).

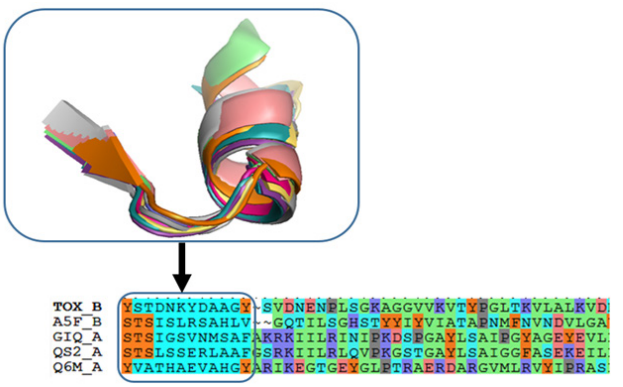
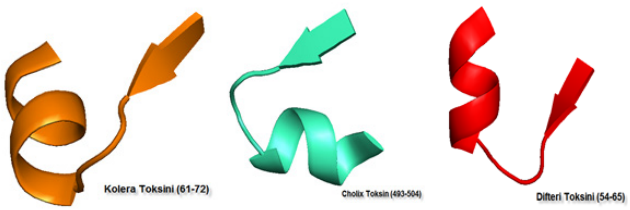


Figure 7: Comparison of Toxin Groups

As a result of the analysis on toxin groups, it was found that the region of approximately 12 acids, starting with Y (Tyrosine) and ending with Y or starting with STS (Serine-Threonine-Serine) amino acids, is on the active site (Figure 8 and 9). In addition it was concluded that a common motif which may occur in this region may be the region that binds to NAD.



Cholera Toxin (61-72) Cholix Toxin (493-504) Diphteria Toxin (54-65)

Figure 8: Active sites recognizing NAD, which start with Y amino acid and also end with Y amino acid belonging to the ADPRT group.

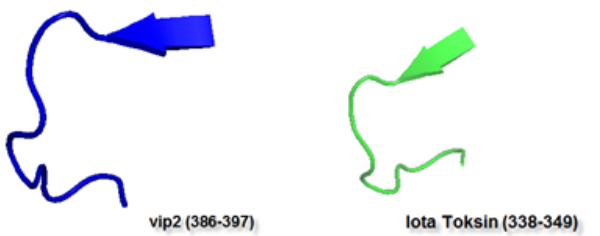


Figure 9: Active sites recognizing NAD, which start with the STS amino acid sequence belonging to the ADPRT group.

At the end of the study, the regions most likely to interact with NAD from the ADPRT groups and the amino acid sequences belonging to these regions were determined to be used in future theoretical and experimental studies (Table 4). As a result of the study, it was theoretically determined that the regions of STS (Ser-Trp-Ser)-10/12 amino acids (starting with Serine-Tryptophan-Serine and taking 10 amino acids) have a structural conformation that recognizes NAD.

Table 4: Regions most likely to interact with NAD from ADPRT groups				
PDB_Id	**Resolution (A)**	**ADPRT**	**Length**	**ADPRT - INTERACTION SERIES**
2A5F	2.02	Kolera Toksini	12	^{61}- STSISLRSAHLV-^{72}
1GIQ	1.80	Ioto Toksin	12	^{336}-STSIGSVNMSAF-^{347}
1QS2	2.70	VIP2	12	^{386}-STSLSSERLAAF-^{392}
1TOX	2.30	Difteri Toksini	12	^{54}-YSTDNKYDAAGY-^{65}

In order to examine the information which was obtained theoretically in our study, an experimental study was carried out on commercially available cholera toxin (sigma-C8052). The sample, which was confirmed to be cholera toxin by electrophoretic processes, was partially digested with trypsin, and then it was separated into fragments by passing through a spherical s-100 column to be cut (Figure 10).

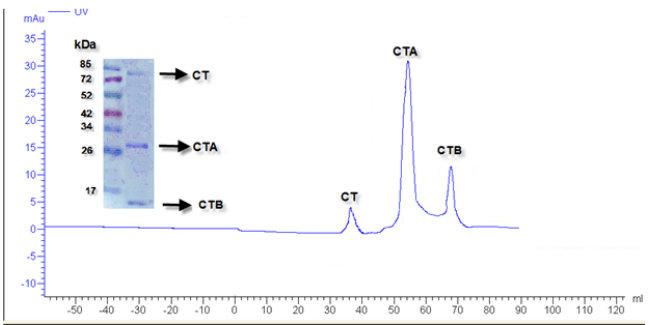


Figure 10: Decomposition of cholera toxin into fragments. A. (1) Protein weight marker, (2) After toxin clipping, was eluted in (10 µg) SDS/PAGE. B. Cholera toxin (0.2 mg), which was partially digested with trypsin as described in the methods, was separated in sephacryl S-100 chromatography. Flow rate 0.8 ml/min, sample volume 0.5 ml. Measurement A280 nm.

The toxicity of the CTA part of the cholera toxin was determined on the HUVEC cells (Figure 11). CTA was tested by thermal shift assay, which is a protein-ligand interaction method. Fluorescent-based thermal shift experiment was carried out as mentioned in the materials and methods. The interaction of the cholera toxin fragment CTA-NAD was examined. For each NAD concentration, a denaturation curve was created in the RT-PCR device by increasing the temperature, and melting degrees (Tm) were calculated. The thermal stability of CTA was found to increase when interacting with NAD (Figure 12). Based on the thermal stability graphs measured from the linear region after the CTA-NAD interaction, Tm values were calculated from the Boltzman equation with GraphPad and Excel (Figure 13).

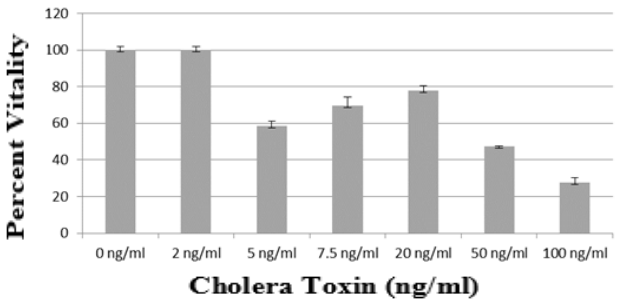


Figure 11: Cholera Toxin 24 hour % viability test. Viability was measured with MTT.

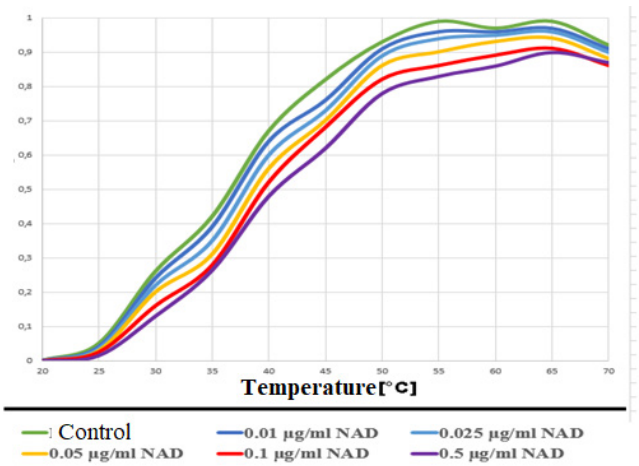


Figure 12: The interaction of cholera toxin CTA-NAD was tested by thermal shift assay. After the application of 10 µg/ml CTA1 and increasing concentrations of NAD in the presence of SYPRO Orange, the fluorescent intensity was measured at a wavelength of 580 nm for 10 seconds (0.5 °C/15 sec) at 0.5 °C between 20 °C and 90 °C. Nad was not applied in the control.

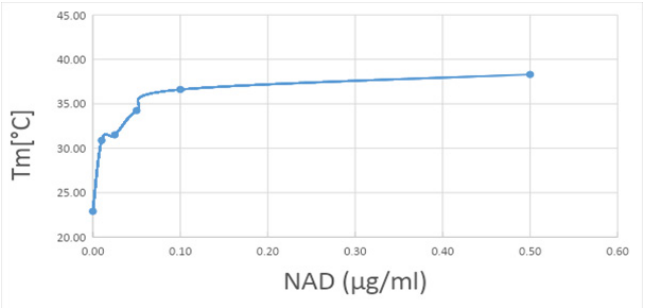


Figure 13: After the CTA-NAD interaction, Tm values from the measured thermal stability graphs were calculated with GraphPad and Excel. In the table, the semi-denaturing temperature (Tm) values obtained by calculating from the linear region were calculated by using the Boltzman equation.

Vibrio Cholerae secrete Cholera Toxin and also CT is carried extracellularly by the system which is called the type II secretion system. This system contains more than a dozen interacting proteins and it ensures that toxin and other proteins such as extracellular enzymes are exported from the periplasm through the outer membrane (17). The signification of CT is regulated by several transcriptional activators controlled by the V cholerae "quorum-sensing system"(18). Whereas the expression of CT increases at low cell densities, the quorum-sensing system downregulates CT sythesis at high cell densities. The key step for intoxication is the entry of CTA into the cell cytosol because the ADP ribosylation of the trimeric Gsα component of AC is catalyzed by CTA. The ADP-ribosylation factors (ARFs) known as a family of essential and ubiquitous G proteins activate this enzymatic reaction allosterically. The crystal structures of a CTA/ARF6-GTP complex show that the binding of ARF activator causes remarkable changes in CTA loop regions which enable the nicotinamide adenine dinucleotide (NAD^+) substrate to bind to the active site (19). ADPRT is a better defined toxin group than other toxin groups in terms of both its structure and effect. In particular diphtheria toxin from this group is divided into two parts after limited proteolytic digestion. The toxin consists of fragment A (FA) with enzymatic function (ADP-ribosyltransferase), corresponding to its N-terminal point, and fragment B (FB), which allows holotoxin to bind to the cell (20). The enzymatic part (FA) of the toxin reaches the cytoplasm in the endocytic process. FA entering the cell causes inhibition of protein synthesis, DNA splicing, destruction of the actin skeleton, and apoptosis (21). CT group toxins are the structures that cause apoptosis or necrosis in the cells which they have affected by targeting various essential proteins in host organisms. Although ADPRT enzymes display a different diversity of functions and low sequence identities, they share common structural and functional features. Firstly, they catalyze a common reaction, namely ADP-ribosylation. Secondly, they have structurally similar catalytic sites that bind NAD+. In our study we investigated the common NAD binding motifs of CT, a member of the ADPRT family, which also occurs in other members of the family. At the end of our study, as stated in the findings, we found a region of 12 amino acids. We classified this region into two groups. These are the regions starting with Y- [10 amino acids] – Y tyrosine and ending with tyrosine in the first group, and the sequences starting with STS- [9 amino acids] Serine-Threonine-Serine in the second group. Although the sequences of non-common amino acids of these regions vary, we believe that their three-dimensional structures are similar and that these common regions are important in the recognition and catalysis of NAD. Our experimental studies showing the parts containing the catalytic regions determined as a result of the theoretical studies also confirm these results. In the context of protein-protein, protein-ligand interactions, the affinity constants of ADP-ribosylating toxins (diphtheria and cholera) with NAD are known. We demonstrated this interaction for the first time with thermal shift assay (TSA) studies, which have found significant use in recent years. After ligand binding to native protein, the resistance to thermal effects increases. Tm values from the denaturation curves after NAD binding were determined according to the Boltzman equation. As the affinity of the ligand to the protein increases, the denaturation temperature increases. By using this method we experimentally observed that the amount of CT binding also increased, with the increasing concentration of CT. Our work was supported by TUBITAK as project number 113S334.

CONCLUSION

In this study an important member of the ADPRT family and CT was simulated using docking software. In consequence of theoretical analyses, we provided an insight into the interaction of the structure with NAD by anticipating the binding of this enzyme to NAD and determining that it has a common structural pattern with DT and CT enzyme groups. CT binds to NAD with 12 amino acids called 61- STSISLRSAHLV-72. That was verified experimentally. Our data showed that the three-dimensional structures of CT and ADPRT are similar although their sequences vary widely. The interaction mechanisms and protein structures of CT and DT shared similarity in catalytic domains whereas they showed differences in substrate proteins.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Biochemistry and Molecular Biology / Biyokimya ve Moleküler Biyoloji

Gram Stain Prediction with Machine Learning Techniques Using Biochemical Parameters in ICU Patients with Urinary Tract Infection

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ABSTRACT

Purpose: The aim of this study was to develop a useful algorithm based on complete blood count (CBC), urinalysis, and biochemical parameters that could be an alternative to Gram staining in the prediction of UTI and the determination of initial antibiotic treatment in ICU patients.

Methods: All the specimens included in the study were obtained from ICU patients and were subjected to Gram staining in the laboratory. Simultaneously, CBC, urinalysis, and biochemical tests were performed for each specimen. A classification based on biochemical parameters was performed for the estimation of Gram-negative and Gram-positive bacteria, as an alternative to Gram staining.

Results: Classification was achieved using multiple classification systems including Artificial Neural Networks (ANN), Support Vector Machine (SVM), the K-Nearest Neighbors (KNN), and Decision Tree Language (DTL) and the best classification performance was achieved by ANN, with an accuracy of 84.6%, a sensitivity of 88.5%, and a specificity of 73.5%.

Conclusion: The high specificity and accuracy of the algorithm indicated that this algorithm can be effectively used in the selection of empirical antibiotic treatment for ICU patients with UTI and can provide more advanced and technological opportunities by combining laboratory parameters with machine learning techniques.

Keywords: Gram Stain, Laboratory, Machine Learning, Urinary Tract Infections

İdrar Yolu Enfeksiyonu olan Yoğun Bakım Hastalarında Biyokimya Parametreleri Kullanarak Makine Öğrenmesi ile Gram boyama tahmini

ÖZET

Amaç: Bu çalışma, yoğun bakımda yatan ve idrar yolu enfeksiyonu bulunan hastalarda başlangıç tedavi seçimine rehberlik etmek için Gram boyamaya alternatif olabilecek, biyokimya tetkikleri ile oluşturulmuş makine öğrenmesi algoritmalarının etkililiğine odaklanmıştır.

Yöntem: Çalışmaya alınan örnekler laboratuvardan Gram boyama isteği yapılmış ve Gram boyamaya eş zamanlı TİT, CBC ve CRP isteği yapılmış 203 yoğun bakım hastasından geriye yönelik oluşturulmuştur. Çalışmada, biyokimya laboratuvar parametreleri kullanarak Gram boyamaya alternatif, Gram-negatif ve Gram-pozitif bakteri tahmini için sınıflandırma yapılmıştır.

Bulgular: Sınıflandırmada ANN (Artificial Neural Networks), SVM (Support vector machine), KNN (K-Nearest Neighbors), DTL (Decision Tree Learning) gibi birçok sınıflandırıcı kullanılmış olup, en yüksek sınıflandırma başarısına ANN ile ulaşılmıştır. Sınıflandırma sonucu ANN ile %84.6 Acc, %88.5 Sn, %73.5 Sp değerlerine ulaşılmıştır.

Sonuç: Özellikle algoritmanın yüksek özgüllüğü ve doğruluğu, yoğun bakım hastalarında idrar yolu enfeksiyonu ampirik antibiyotik tedavisi seçiminde kullanılabileceğini, laboratuvar testlerinin makine öğrenmesi metotları ile harmanlanarak daha gelişmiş ve teknolojik imkanlar sağlayabileceğini göstermiştir.

Anahtar sözcükler: İdrar yolu enfeksiyonu, Makine Öğrenmesi, Biyokimya, Gram boyama, Yoğun Bakım Hastaları

Urinary tract infections (UTIs) are the primary cause of sepsis in an intensive care unit (ICU) and urosepsis can be seen in up to 16% of ICU patients. Catheter-associated UTI is the most common cause of ICU-acquired infection and accounts approximately for 40% of hospital-acquired infections (1-5). Additionally, UTI has been shown to be the most common infection in ICU patients (4).

Prompt treatment with an effective antibiotic therapy will decrease the mortality risk in patients suspected of (not with) sepsis (6). In this regard, appropriate antibiotic selection criteria are highly important in terms of both treatment and antibiotic resistance.

Gram-negative bacteria (GNB) are the most common organisms causing ICU-acquired UTI. Primary risk factors in these patients include catheterization, length of stay in ICU, ineffective antibiotic use, and gender. In the empirical antibiotic therapy in patients with suspected ICU-acquired UTI, the initial choice of antibiotics usually covers GNB and includes aminoglycosides, β-lactam, and a β-lactamase inhibitor or carbapenem antibiotics. However, it often does not cover Gram-positive bacteria (7).

In the patients with ICU-acquired UTI, the selection of appropriate organism-based antibiotics can be life-saving at the early stages of the infection. Moreover, it can also preserve the effectiveness of existing antibiotics, thereby slowing down the development of antibiotic resistance which has increased in recent years. The World Health Organization (WHO) published a global action to optimize the use of antimicrobial agents and to improve awareness and understanding of antibiotic resistance. In addition, although administering empirical antibiotics within a few hours after hospital admission reduces mortality in critically ill patients, it may have adverse effects on broad-spectrum antibiotic resistance (7-10).

Although culture specimens obtained from ICU patients are the golden standard for identifying organisms responsible for UTI, it takes approximately 48-72 hours to obtain the results of culture and antibiotic susceptibility tests. Accordingly, shortening this time period and initiating the initial effective and rapid treatment according to Gram staining results is highly important.

Transportation of the specimens obtained for Gram staining to the laboratory and their processing and microscopic examination are time-consuming activities that increase laboratory workload. For this reason, careful and early detection of the infection and prompt initiation of appropriate antibiotic treatment for the causative agent will increase the success of the treatment and will also reduce the complications.

Artificial intelligence can be effective in the improvement of healthcare services due to its effect on modeling and decision-making processes. In addition to the growing importance of evidence-based medicine applications, various machine learning systems can perform clinical diagnosis and even offer treatment recommendations (11). The number of promising studies conducted on this issue is increasing continuously (12,13).

The aim of this study was to develop a useful algorithm based on complete blood count (CBC), urinalysis, and biochemical parameters that could be an alternative to Gram staining in the prediction of UTI and the determination of initial antibiotic treatment in ICU patients and could provide faster results and thus could reduce the workload of laboratories. This algorithm will be a cost-effective technological alternative to Gram staining and culture analysis and even to the algorithms used for predicting antibiotic resistance and will also shed light on studies investigating personalized prediction algorithms. Additionally, to our knowledge, there has been no study reporting on the determination of bacterial species in UTI by machine learning methods using CBC, urinalysis, and biochemical parameters.

MATERIALS AND METHODS

This study was conducted through a collaboration between Elazig City Hospital Biochemistry and Microbiology Departments and Fırat University Software Engineering Department. This retrospective study was performed by analyzing the data obtained from the laboratory information system in Elazig Fethi Sekin City Hospital that had been recorded between March 2019 and May 2020.

All the specimens included in the study were obtained from ICU patients and were subjected to Gram staining in the laboratory. Simultaneously, complete blood count (CBC), urinalysis, and biochemical tests were performed for each specimen. Patients with negative Gram staining results and patients whose biochemistry tests were not conducted at the same time with Gram staining were excluded from the study. The 202 patients included in the study comprised 108 women (age, 18-97 years) and 94

men (age, 18-95 years). The demographical characteristics of the patients are shown in Table 1.

Table 1. Demographical characteristics of the patients

	Min	Max	Median	Interquartiles (25%-75%)
AGE	18	97	76	59,2-83
WBC	4,6	31,2	10	8,0-12,6
NEU	1,86	29,8	6,57	4,96-9,47
LYM	0,2	8,51	1,66	1,10-2,48
MON	0,16	3,24	0,71	0,55-1
EOS	0,001	4,15	0,14	0,04-0,3
BAS	0,001	0,69	0,06	0,04-0,1
USGT	1.002	1.033	1.013	1.011-1.018
Ph	5	9	6,5	5,5-7,5
CRP	1,07	458	62,05	23,6-102

WBC: White Blood Cell, NEU: Neutrophil, LYM: Lymphocyte, MON: Monocyte, EOS: Eosinophil, BAS: Basophile, USGT: Urine Spesific Gravite Test, CRP: C Reactive Protein

Complete blood count (CBC) was performed using a Unicel DXH-800 hematology analyzer (Beckman Coulter, Inc., Brea, CA, USA). CRP levels were analyzed by the spectrophotometric method using an Image 800 analyzer (Beckman Coulter, Inc., Brea, CA, USA). Urinalysis were performed using the Iris iQ200 Sprint automated urine microscopy analyzer (Beckman Coulter, Inc., Brea, CA, USA). Table 2 presents the reference ranges for CBC, urinalysis, and biochemical parameters.

Table 2. Reference ranges

Parameter	Variable	Reference Range
CBC	WBC	3.6-11 (10^9/L)
	Neutrophil count	1.7-7.6 (10^9/L)
	Lymphocyte count	1.0-3.2 (10^9/L)
	Monocyte count	0.3-1.1 (10^9/L)
	Eosinophil count	0-0.5 (10^9/L)
	Basophile count	0-0.1 (10^9/L)
Urinalysis	Density	1.005-1.025
	pH	4.5-8
	Nitrite	Negative
	Erythrocyte	0-4
	Leukocyte	0-4
Biochemical	CRP	0-8 mg/L

WBC: White blood cell count, CRP: C-reactive protein

The extent of positive Gram staining was estimated using the measurements of CBC, urinalysis, and biochemical parameters. To achieve this, a database was created based on the collected data and then classification was performed according to the extent of intensity of Gram staining using 12 input parameters (CBC, urinalysis, and CRP). We selected features that are known to be associated with urinary tract infection and that are made up of routine and easily accessible biochemistry laboratory parameters that are studied daily. The classification was achieved using multiple classification systems including Artificial Neural Networks (ANN), Support Vector Machine (SVM), the K-Nearest Neighbors (KNN), and Decision Tree Language (DTL) and the best classification performance was achieved by ANN. Figure 1 illustrates the flow diagram used for the classification.

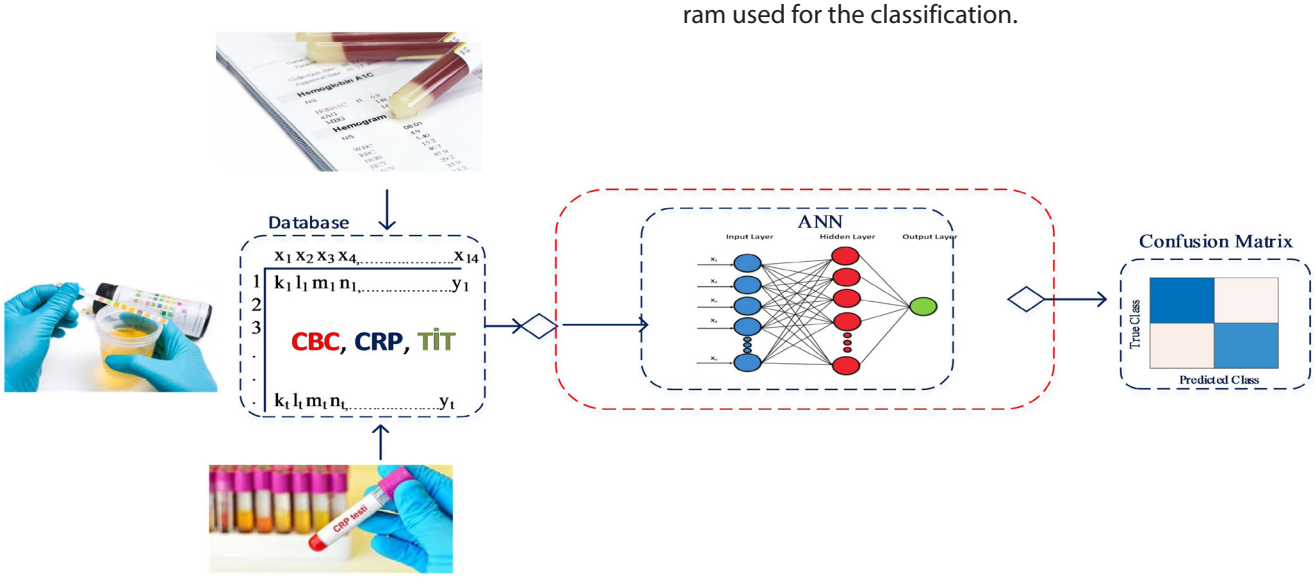

Figure 1. Flow diagram used for classification

Classification

Artificial Neural Networks (ANN) is an information processing technology imitating the working and learning skills of the human brain (14). To date, numerous algorithms related to ANN have been developed and used in many areas. In the present study, the CBC, urinalysis, and CRP values were classified according to the families of the bacteria that caused infection in the urine culture using the Backpropagation Neural Network.

Backpropagation is a widely used method for training parameters in ANN. The generalized delta rule is a method that allows some of the difference (error) between the target values and the network output (error) to be reflected back to each training cell and thereby to change the weights according to the error and to repeat this process for a certain number of times during the training of backpropagation networks, in attempts to obtain the lowest error possible (15). Figure 2 illustrates the structure of backpropagation neural network.

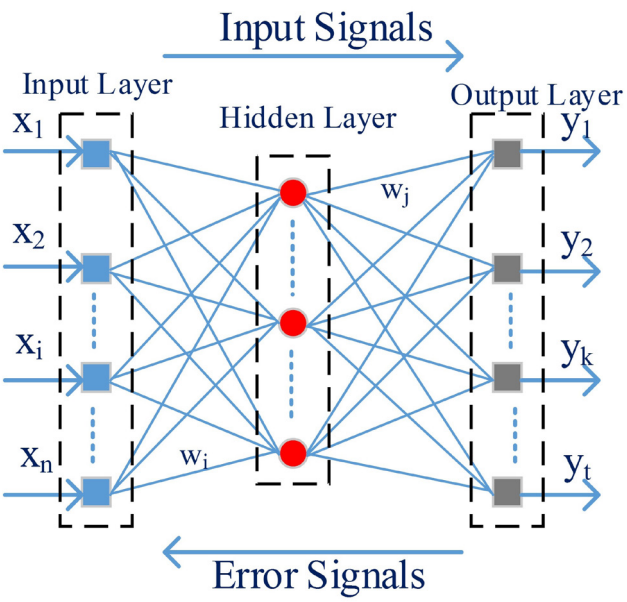

Figure 2. Multilayer backpropagation neural network

The k-fold cross validation was used to minimize distribution-related errors in the training and testing phase of the model proposed in the study. To achieve this, the training dataset was randomly divided into k number of subsets, whereby k-1 number of subsets were used for training and the remaining one subset was used for testing. The same procedure was repeated k times and the values obtained at each repetition were summed up and averaged and then the performance of the model was calculated. Figure 3 illustrates the structure of ANN.

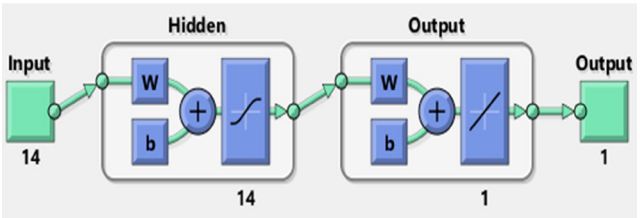

Figure 3. Structure of the ANN model used in the study

Performance evaluation

The performance of the classification was assessed using the following parameters: Sensitivity, Specificity, Precision, Negative Predictive Value (NPV), False Positive Rate (FPV), False Discovery Rate (FDR), False Negative Rate (FNR), Accuracy, and F score. Table 3 (16).

Table 3. Performance evaluation criteria

Measure	Formula
ACC	(TP + TN) / (TP + TN + FN + FP)
SN	TP / (TP + FN)
SP	TN / (TN + FP)
FPR	FP / (TN + FP)
PREC	TP / (TP + FP)
F1	2 * PREC * REC / (PREC + REC)

Acc: Accuracy, SN: Sensitivity, SP: Specificity, FPR: False positive rate; PREC: Precision: F: F score; TP: True positive: TN: True negative; FP: False positive; FN: False negative

Data Analysis

The models used in the study were tested in the Matlab R2018b (The MathWorks, Inc. Cambridge, United Kingdom) platform on a computer with an i7 9750 H CPU, 2.6GHz, 16 GB RAM and Geforce GTX 1050 gCPU. Laboratory data analysis (laboratory characteristics of patients) was performed on Jupyter Notebook using Python 3.0 (Python Software Foundation, Oregon, USA) program with Pandas library.

RESULTS

In the present study, a classification model using ANN, SVM, KNN, and DTL with the inputs obtained from biochemical parameters was proposed as an alternative to Gram staining for the prediction of UTI in ICU patients. Table 4 presents the performance of each classifier.

Table 4. Performance of the classifiers used in the study

	SN	SP	PREC	ACC	F1
ANN	0.8859	0.7358	0.9041	0.8465	0.8949
SVM	0.7684	0.8333	0.9865	0.7723	0.8639
KNN	0.7228	0.8333	0.9865	0.7290	0.8343
DTL	0.7593	0.4250	0.8425	0.6931	0.7987

SN: Sensitivity, SP: Specificity, PREC: Precision, Acc: Accuracy, F: F score

As seen in Table 3, ANN had the highest accuracy (84.6%) and sensitivity (88.5%) values. Additionally, although SVM and KNN had the highest precision value (98.7%), ANN had the highest F1 value (89.4%).

DISCUSSION

The present study investigated the effectiveness of an artificial intelligence algorithm of initial treatment selection which was created with biochemical parameters and was utilized as an alternative to Gram staining in ICU patients with UTI. This diagnostic algorithm, which was created based on urinalysis, CRP and CBC results will guide empirical treatment and the findings of the study will also provide clinicians a different alternative in the selection of broad-spectrum antibiotics without increasing the risk of treatment failure.

Antibiotic resistance remains a serious public health problem (17). Accordingly, rapid and cost-effective procedures developed in line with technological advancements are needed to decrease redundant use of broad-spectrum antibiotics and thereby to reduce the development of antibiotic resistance. The diagnostic algorithm developed in the present study can be used in ICUs as a useful high-potential tool for the selection of broad-spectrum antibiotics.

Culture analysis performed for detecting the causative agent within several days after hospitalization is the golden standard for the treatment of patients suspected with infection. However, in such patients, considering the benefits of prompt treatment, empirical antibiotic therapy is the first-line treatment particularly in patients hospitalized in ICU. Additionally, empirical antibiotic therapy has also been shown to reduce mortality in such patients (21-24).

An infection caused by multi-resistant Gram-negative bacilli results in significantly higher mortality than an infection caused by other pathogens; therefore, knowledge of the morphology of the organism in the initial treatment plan is of paramount importance. In contrast to studies reporting on a moderate correlation between Gram staining and culture (19,20), Yoshimura et al. (18) examined the effect of Gram staining on initial therapy in patients with ventilator-associated pneumonia and provided the first evidence that Gram staining could reduce the use of broad-spectrum antibiotics.

Although enteric bacteria (especially E. coli, Gram-negative) are responsible for most UTIs, there are a wide range of pathogens causing UTI. Of note, Staphylococcus saprophyticus, Enterococcus faecalis, and Streptococcus agalactiae are the most common causes of Gram-positive UTI. On the other hand, antibiotic choices of Gram-positive and Gram-negative bacteria are different from each other (25,26). Accordingly, it is highly important to develop diagnostic options that can show these differences and start treatment promptly to narrow down the treatment options. In such patients, considering the benefits of prompt treatment, empirical antibiotic therapy should be the first-line treatment particularly in patients hospitalized in ICU. Additionally, empirical antibiotic therapy has also been shown to reduce mortality in such patients (22,27,28).

The algorithm developed in the present study indicated that UTI can be predicted in ICU patients based on their routine CBC, urinalysis, and biochemical parameters with no need for Gram staining. Accordingly, this algorithm is appears to be a viable diagnostic option since it is highly cost-effective and was developed with a remarkably smaller number of datasets.

In our study, ANN, SVM, KNN, and DTL were used for classification. Since the system parameters in models such as ANN are problem-dependent, it cannot be predicted as to which of the parameters (e.g. number of layers in Multilayer Perceptrons [MLP], number of neural processors in hidden layers, learning coefficient) will provide an optimal result. Therefore, a good learning rate to be provided by these parameters must be discovered via trial and error. On the other hand, a comparison between/among classifiers are not recommendable, although an algorithm is likely to have a propensity for a particular problem.

Accuracy is calculated as the percentage of correctly classified instances to the total dataset; therefore, accuracy alone may not be sufficient in imbalanced classes. Sensitivity measures how well a test can identify true positives for people with the condition being tested, while specificity measures the ability of a test to produce an accurate negative result for people who do not have the condition being tested. Accordingly, all these three parameters should be evaluated together to obtain the best classification performance. High specificity helps prevent misunderstanding and avoidable unnecessary interventions (True Negative), while a highly sensitive test is needed particularly in ambiguous diagnosis or in cases of early disease (True Positive). The F1-score uses the harmonic mean instead of the arithmetic mean so as not to ignore extreme cases. For this reason, the F1 score was included in the evaluation metrics.

Our results indicated that the algorithm developed in the present study based on routine CBC, urinalysis, and biochemical parameters could be a useful alternative to Gram staining for the prediction of UTI in ICU patients.

CONCLUSION

Although the Gram staining technique was developed by Hans Christian Joachim Gram in the 1880s (29), it is commonly used in bacteriology laboratories. However, the time from the admission of the specimens to the staining and interpretation processes is remarkably long and depends on the technician's/laboratory specialist subjective interpretation even when there is only one specimen to be analyzed. Our findings indicated that Gram staining could be conducted with different alternatives and these alternatives may help ameliorate the laboratory workload. Accordingly, we consider that our study provides advanced and technological opportunities for the bacterial classification performed with Gram staining by combining biochemical tests with machine learning methods. We also believe that the study will shed light on future studies on this subject.

Ethical Consideration

The study protocol was approved by Fırat University Ethics Committee (Approval No.: 2020/08-41-486, Date: 29 April, 2020).

Conflict of Interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Emergency Medicine / Acil Tıp

Relationship between Low Eosinophil Level at Presentation and Disease Severity and Mortality in Covid-19 Patients

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ABSTRACT

Purpose: Early and rapid diagnosis of COVID -19 is vital to reduce mortality. It has been shown that detecting low eosinophil levels at the first application in suspected cases of COVID -19 can be used to diagnose the disease and predict its severity. In the present study, we aimed to determine the usability of this parameter in the early diagnosis of COVID-19 and treatment planning by evaluating at the eosinophil levels.

Methods: As a retrospective study included those who were admitted to the hospital, with the pre-diagnosis of COVID-19. Demographic characteristics, laboratory values, radiological images and clinical follow-up were scanned through the hospital system. All statistical analysis was done using the SPSS v25 software.

Result: Thirty-seven women (30.08%) were included in our study. The average age was 49.13, and we found the most cases in the 26-65 age range. The most common symptoms were cough 51.21%, dyspnea 26.8% and fever 26.39%. Hypertension was detected 21.95% and diabetes 12.19% as comorbid diseases. A computed tomography scan showed viral pneumonia in 50.40% (n:62) of our cases. 49.59% (n: 61) had Polymerase chain reaction positive results and 39.02% (n: 48) of our cases had both viral pneumonia in the CT scan and PCR (+). We found that dead patients had significant lower eosinophil levels.

Conclusion: Eosinophil level may support the diagnosis in suspected cases of Covid-19 and maybe a warning that the clinical picture may progress seriously.

Keywords: Covid-19, Eosinopenia, Severity

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Covid-19 Hastalarında Başvuru Anında Düşük Eozinofil Düzeyi ile Hastalık Şiddeti ve Mortalite Arasındaki İlişki

ÖZET

Amaç: Covid-19 tanısının erken ve hızlı tespit edilmesi mortaliteyi azaltmak için önemlidir. Eozinofil düzeyinin Covid-19 şüpheli vakalarda ilk başvuru anında düşük tespit edilmesinin hastalığın tanısını koymada ve ciddiyetini öngörebilmede kullanılabileceği belirtilmiştir. Çalışmamızda vakalarımızın eozinofil düzeyine bakarak bu parametrenin Covid-19 erken tanı ve tedavi planlanmasında kullanılabilirliğini saptamayı amaçladık.

Gereç ve Yöntem: Retrospektif olarak yapılan bu çalışmaya Covid-19 ön tanısı ile yatan vakaları aldık .Hastaların demografik özellikleri, laboratuar değerleri, radyolojik görüntüleri ve klinik takip bilgileri hastane bilgisayar sisteminden tarandı. SPSS 25 programı ile istatistik hesapları yapıldı.

Bulgular: Hastalarımızın 37'si kadındır (%30,08). Yaş ortalaması 49,13 ve en çok vakayı 26-65 yaş aralığında tespit ettik. En sık semptom olarak öksürük %51,21, dispne %26,8 ve ateş %26,39 görüldü. En sık görülen komorbid hastalık hipertansiyon %21,95 ve diyabet %12,19. Vakalarımızın %50,40'ın da (n:62) bilgisayarlı tomografisin de viral pnömoni (konsolüdasyon, buzlu cam opasiteleri), %49,59'unda (n:61) Polimeraz Zincir Reaksiyonu pozitifliği ve %39,02'sin de (n:48) ise hem bilgisayarlı tomografi'de viral pnömoni hem de PCR (+) tespit edildi. Vefat eden vakalarımızda ilk başvuruda eozinofil düzeylerinde düşüklüğü tespit ettik.

Sonuç: Eozinofil düzeyi düşüklüğü Covid-19 şüpheli vakalarda tanıyı destekleyebilir ve klinik tablonun ciddi seyredebileceği ile ilgili bir uyarı olabilir.

Anahtar kelime: Covid-19, Eozinopeni, Mortalite

In December 2019, SARS-CoV-2, an enveloped RNA virus, was detected in China as well as increasing pneumonia cases. The disease caused by this virus was named COVID-19 by the World Health Organization (1). In Turkey, on January 22, 2020, the Ministry of Health COVID-19 Scientific Committee was established, and the encounter measures, infection control-isolation and treatment processes were planned (2). In addition to fever, dry cough, dyspnea and malaise, atypical symptoms such as gastrointestinal system findings and anosmia can also be observed in these patients (3). Besides symptomatic cases, there are also asymptomatic cases (4). Asymptomatic cases may pose a risk for the spread of the disease (5,6). Mortality increases in patients who are 65 years old and above, chronic disease and immune system weakness (7). Hypertension (HT) and diabetes mellitus (DM) are the most common comorbid diseases. Studies have shown that DM increases the need for intensive care follow-up, especially in patients (8,9). It is important to reduce the spread rate of COVID-19, which causes severe respiratory distress and makes an early diagnosis to decrease mortality (10). Studies suggest that hematological parameters can be used for diagnosis and evaluation of the treatment given in these patients (11). It has been stated that detection of low neutrophil, lymphocyte, hemoglobin and eosinophil levels in the complete blood count at the first application of the patient may strengthen the diagnosis of COVID-19 (12). The eosinophil is a hematological parameter used for diagnosis and treatment in many diseases with its pro-inflammatory effect, which is active in the tissue and circulation. The immune-regulatory and antiviral effect of eosinophil has also shown (13,14). Eosinophil level can be measured easily and quickly from a complete blood count. In a study conducted in patients with a diagnosis of COVID-19, it has shown that low eosinophils may be linked to increased inflammatory response and increased viral load may trigger eosinophil granulated protein consumption by reducing the level of IL-5 released from CD8 T cells, leading to low level of eosinophil (15,16). We evaluated the eosinophil levels of patients who hospitalized in intensive care or in service with the diagnosis of COVID-19. We aimed to evaluate the disease's progression by looking at the usability of initial eosinophil levels in early diagnosis and the eosinophil levels after treatment.

MATERIAL AND METHOD

This study was approved by Ethical Committee of Ankara Numune Training and Research Hospital Ethics Committee (No: E1-20-598). We enrolled all cases in Ankara Numune Training and Research Hospital Emergency Department between 15/04/2020 and 22/04/2020. Patients were 18 years old or older with polymerase chain reaction (PCR) positivity and/or lesions compatible with COVID-19 viral pneumonia in computed thoracic tomography. In the present study, we retrospectively scanned the patients' demographic characteristics (age, sex), contact history, smoking situation, symptoms at the time of admission, comorbid diseases, admission information, length of stay, computed tomography (CT) (consolidation, ground-glass opacity), blood and PCR results from the records in the hospital computer system. We analyzed the data using the SPSS v.25 program. Statistical analyzes were performed with a Mann-Whitney U test. Statistical significance was evaluated with a 95% confidence interval. $p < 0.05$ was considered statistically significant.

RESULTS

One hundred twenty-three cases were included in the study. 69.91% of our cases were men. The average age was 49.10. 62.60% of our cases did not contact patients diagnosed with COVID-19 (Table 1). % 60,16 of our patients do not have a chronic disease. % 19,51 of cases smoke. A Mann-Whitney test indicated that eosinophil levels was lower at the first admission for patient who had a positive PCR results (Mdn = 0.5), than for patients who had a negative PCR results (Mdn: 0.7, p=0.05). Even though eosinophils levels were greater for patients who discharged (Mdn = 0.6) than for patients who died (Mdn = 0.4), this difference was not statistically significant (p = .908).In 50,40% (n:62) of our cases, lesions consistent with viral pneumonia (consolidation, ground-glass opacity) were observed on CT. 49.59% (n: 61) were positive for PCR, and 39.02% (n: 48) were both positive for CT, viral pneumonia and PCR. Cough 51.21%, was the most common symptom while dyspnea 26.80% and other symptoms %27,64 (gastrointestinal complaints) were also present. HT 21.95% and DM 12.19% were the most common chronic diseases (Table 2). Those with co-morbid diseases have longer hospital stays (MDN = 10.5, p=0.003). Hospitalization periods were also greater for patients who had a positive PCR results (Mdn = 9) than for patients who had a negative PCR results (Mdn = 7, p=.015) Nevertheless, hospitalization periods were not statistically significant between patients who discharged (Mdn = 8) than for patients who died (Mdn = 6, p=.155). 71.5% (n: 88) of our cases were followed by hospitalization and 28.45% (n: 35) of them in the intensive care unit. = 0.069). In our study patients who died had statistically significant higher neutrophil, D-dimer, ferritin, white blood cell (WBC) and C-reactive protein (CRP) levels than patients who discharged. 91.05% (n: 112) of our cases were discharged. The average age of the discharged cases was 73, and 68.57% (n: 24) were male. The eosinophil levels of

our patients hospitalized in intensive care and died were also low, but when we compared the eosinophil levels of the patients discharged, we found no statistical difference (p: 0, 908) (Table 3).

Table 1: Data of gender, age, contact	
Gender	
Male	69,91% (n:86)
Female	30,08% (n:37)
Age	
18-25	13,82% (n:17)
26-45	39,02% (n:48)
46-65	23,57% (n:29)
≥ 65	23,57% (n:29)
Contact	
Yok	62,60% (n:77)
Var	37,39% (n:46)

Table 2: Symptoms and other Diseases	
Symptom	
Cough	51,21 % (n:63)
Other	27,64 % (n:34)
Dyspnea	26,80 % (n:33)
Fever	24,39 % (n:30)
Anosmia	2,40 % (n:3)
Other Diseases	
None	60,97% (n:75)
Hypertension	21,95% (n:27)
Diabetes	12,19% (n:15)

DISCUSSION

Since December 2019, COVID-19 infection has been a cause of rapid mortality worldwide, especially in elderly patients. Admissions to intensive care units with respiratory distress have also increased. Patients hospitalized in intensive care have a high mortality rate (17,18). In this study our patients who were hospitalized in intensive care were mostly old and male. We interpreted this situation in our country that men over the age of 65 are mostly together and outside of the home. In the literature in which there are many male cases in the same situation (19). Our patients are most frequently applied to the emergency department with symptoms such as cough, dyspnea, fever and nausea, vomiting, and diarrhea, which is consistent with other studies (20). To diagnose COVİD-19 patients, thorax CT and PCR test are requested. However, in some cases, CT cannot be taken or an atypical lesion is described. Sometimes the PCR test may be delayed or a repeat test may be required because of insufficient material. We concluded that some people may have had contact with people who were in the early period of the disease or asymptomatic. Catching asymptomatic cases are important to contain the epidemic. Therefore it may be useful to use hematological parameters to detect these patients, especially those in the early stages of infection (21). Eosinophils are produced in the bone narrow and effective immunmodulators in the initiation and spread of some inflammatory processes (22). It has been stated that increased eosinophils in the lung tissue may be a barrier against viral agents (23). In a study suggested that the cause of neutropenia, lymphopenia and eosinopenia is the passage of these cells into the lung tissue, thus causing acute lung injury and ARDS.

Table 3: Relationship between eosinophil ratios and discharged-ex

Discharged* Low Crosstabulation						
			Low	**Normal**	**High**	**Total**
Discharged	**Yes**	**Count**	35	75	1	111
		Discharged	31.5%	67.6%	0.9%	100.0%
		Low	89.7%	92.6%	33.3%	90.2%
		Total	28.5%	61.0%	0.8%	90.2%
	Ex	**Count**	4	6	2	12
		Discharged	33.3%	50.0%	16.7%	100.0%
		Low	10.3%	7.4%	66.7%	9.8%
		Total	3.3%	4.9%	1.6%	9.8%
Total		**Count**	39	81	3	123
		Discharged	31.7%	65.9%	2.4%	100.0%
		Low	100.0%	100.0%	100.0%	100.0%
		Total	31.7%	65.9%	2.4%	100.0%

They stated that the disease might indicate the severity and the monitoring of hematological parameters might be necessary in this case (24). High d-dimer, ferritin, WBC and CRP level can accompany with low eosinophils in COVID-19 (25). Low eosinophil levels may be related to the severity of COVID-19 disease and that eosinophil may be more sensitive than other blood parameters. Besides, studies have demonstrated that decreased eosinophilia levels can support the diagnosis of COVID-19 in cases with typical COVID symptoms and radiologically supported, regardless of lymphopenia (26). It was stated that the increase in eosinophil values with treatment might be beneficial for the progression of the disease (27). In a study, it was shown that the late increase in eosinophil levels, which was low at first in patients with COVID-19, may be determinant for the negative progression of the disease and that we can follow the progression of the disease with serial monitoring of eosinophil levels (28). On the other hand, studies showed that the decrease in eosinophil level will not be associated with adverse clinical progression of the COVID-19 disease. It is said that studies with a large number of cases are needed to evaluate this situation (29).

CONCLUSION

According to our study's data, patients with low eosinophil levels at the beginning were more severe, and we interpreted it as mortality rate. It can be used as a predictive factor for the severity of the Covid-19. This blood parameter can be used to determine the eosinophil level, which can result quickly and diagnose cases suspected to be COVID-19 early and evaluate the treatment process.

Limitation

Our study was done in a single center. We have low number of patients.

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Evaluation of Geriatric Patients Admitted to the Dermatology Outpatient Clinic for Treatment of Facial Dermatosis: A Retrospective Study

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ABSTRACT

Purpose: Skin is the human body's largest organ, and it has essential social, sexual, and psychological roles. Especially the effect of this fact on visible body parts such as face is more prominent. The elderly population is increasing all over the world, and medical treatment for these senior citizens' dermatological complaints is more frequent in Turkey as elsewhere. The aim of this study is to report the age group, gender distribution and dermatological diseases of the geriatric population admitted to our dermatology outpatient clinic, which is a tertiary referral center for any facial skin complaint.

Methods: This retrospective study included 302 patients aged 65 and over with facial skin complaints. The age, disease frequency, gender and localization distribution of the patients were examined. SPSS package program was used for data analysis.

Results: There was a significant difference between the diagnoses groups of the participants in terms of gender and age groups. The most common facial dermatoses in this population examined were basal cell carcinoma (BCC), actinic keratosis (AK), seborrheic keratosis (SK), rosacea, urticaria, and benign skin and skin appendage tumors.

Conclusion: As the geriatric population is increasing all over the world, recognition of skin diseases is becoming increasingly important. Facial dermatoses are especially a concern because of how they affect the appearance and expression of persons in this age group.

Keywords: Basal cell carcinoma, facial dermatosis, geriatrics, rosacea

Yüz Dermatozu Nedeniyle Dermatoloji Polikliniğine Başvurulan Geriatrik Hastalarin Retrospektif Olarak Değerlendirilmesi

ÖZET

Amaç: Deri, insan vücudunun en büyük organıdır ve sosyal, cinsel ve psikolojik rollere sahiptir. Bu durumun özellikle yüz gibi vücudun görünen kısımları üzerindeki etkisi daha aşikardır. Tüm dünyada yaşlı nüfus artmakta ve bu bireylerin dermatolojik şikayetleri tüm dünyada olduğu gibi Türkiye'de de artık daha sık görülmektedir. Bu çalışmanın amacı yüz derisinde herhangi bir şikayet ile üçüncü basamak dermatoloji polikliniğimize başvuran geriatrik popülasyonun yaş grubu, cinsiyet dağılımı ve yüz dermatoz tanılarının değerlendirilmesidir.

Yöntem: Retrospektif çalışmaya yüz bölgesinde dermatolojik şikayetleri olan 65 yaş ve üzeri 302 hasta dahil edildi. Hastaların yaş, hastalık sıklığı, cinsiyet ve lokalizasyon dağılımı incelendi. Verilerin analizi için SPSS paket programı kullanıldı.

Bulgular: Cinsiyet ve yaş grupları açısından katılımcıların dermatolojik tanısal alt grupları arasında anlamlı farklılık saptandı. Çalışmada incelenmiş olan geriatrik popülasyonda en sık görülen yüz dermatozları bazal hücreli karsinom (BCC), aktinik keratoz (AK), seboreik keratoz (SK), rozasea, ürtiker ve benign deri ve deri eki tümörleriydi.

Sonuç: Tüm dünyada geriatrik popülasyonun artmasıyla birlikte deri hastalıklarının tanınması giderek önem kazanmaktadır. Yüz dermatozları, bu yaş grubundaki kişilerin görünüşü ve ifadesini etkilediğinden dolayı endişe verici olabilir ve hastaların tedavi arayışı ile sonuçlanabilir.

Anahtar kelimeler: Bazal hücreli karsinom, yüz dermatozları, geriatrik, rozasea

With the development of health care and technologies, the management strategies of chronic diseases have also increased. The resulting extension of average human life expectancy has thus caused an increase in the elderly population (1). The number of elderly people is increasing day by day all over the world, and it is estimated that one fifth of the entire population will consist of individuals aged 65 and over by 2050 (2). Thus, hospital admissions of elderly people will increase, and it is important to know the diseases specific to this population including the dermatological diseases.

Skin is the human body's largest organ, and it has essential social, sexual and psychological roles in self-expression, the perception of beauty and esthetics. Aging is a physiological process that starts from the mother's womb and is related to many factors. This process affects changes in the skin as it does throughout all organ systems. Wrinkles, coarsening and changes in elasticity occur in the skin, while the frequency of some dermatological diseases increases and/or their presentations change (1). Skin lesions in visible areas such as the face and hands undeniably have considerable negative effects on people (3). It is known that skin diseases of the face, which is the most striking body part at first glance, and other visible areas, lead to increased emotional stress and psychosocial effects (4). Although there are many studies that examine skin diseases and skin changes in the geriatric age group, so far we find no study focusing specifically on facial skin diseases. The aim of this study is to report the age group, gender distribution and dermatological diseases of the geriatric population admitted to our dermatology outpatient clinic, which is a tertiary referral center for any facial skin complaint. We also aimed to evaluate the age, gender, disease frequency and localization of these dermatological diagnoses by grouping the diseases.

MATERIALS AND METHOD

The study was designed retrospectively as a cross-sectional evaluation of a study group consisting of patients admitted to Başakşehir Çam and Sakura City Hospital (education and research hospital) Dermatology Outpatient Clinic between August 31, 2020, and August 31, 2021. Ethics committee approval was obtained from Istanbul Kent University Ethics Committee. Patients aged 65 and over were filtered through the hospital data processing system and their examination notes and diagnoses were reviewed. Accordingly, patients who applied to the Dermatology Outpatient Clinic with facial lesions were included in the study. Thus, disease diagnoses were based on clinical notes and existing pathology reports for malignant, pre-malignant lesions. Age, gender, location of the lesions and diagnosis were recorded. Inclusion criteria for the study were: being ≥65 years of age, applying to dermatology outpatient clinic with complaints in the facial area, and presence of complete data. Patients with missing data and who were consulted from other departments due to facial skin complaints were excluded from the study. After making general diagnoses, these were divided into 10 diagnostic subgroups according to main dermatologic diseases: Allergic / inflammatory dermatoses (rosacea, folliculitis, alopecia areata, angioedema, urticaria and polymorphous light eruption); dermatitis group of diseases (perioral dermatitis, seborrheic dermatitis, atopic dermatitis, irritant contact dermatitis, allergic contact dermatitis, nummular dermatitis, and angular cheilitis); erythematous-squamous diseases (psoriasis and lichen group diseases); cutaneous infections (verruca vulgaris, herpes zoster, herpes simplex infection, tinea faciei, and lupus vulgaris); rheumatological diseases (dermatomyositis, and discoid lupus erythematosus); autoimmune blistering diseases (pemphigus and bullous pemphigoid); benign neoplasia (seborrheic keratosis, pyogenic granuloma, xanthelasma, skin tag, lentigo simplex, other benign skin and skin appendage tumors); premalignant changes (keratoacanthoma, cutaneous horn, actinic keratosis, actinic cheilitis); cutaneous malignancy (Kaposi sarcoma, squamous cell carcinoma, basal cell carcinoma); melanocytic lesions and miscellaneous (melanocytic nevus, hyperpigmentation, lupus pernio, cuperosity, scarring, xerosis, venous lake).

SPSS 22.0 package program was used for data analysis. Frequency values, and mean values of the patients' demographic characteristics were calculated. The frequencies of the facial dermatoses of the patients included in the study were calculated by determining the localization. Pearson Chi-Square test was performed to determine whether the disease diagnoses of the patients included in the study differed statistically by gender and age.

RESULTS

A total 302 patients were enrolled in the study. Their age range was 65-101 with the mean of 73, 8±8, 1 year (mean age ± standard deviation (SD)). Of the patients included in the study, 54% were women and 46% were men. Patients in the 65-74 age range constituted 59% of participants (Table 1).

Table 1. Demographic Frequency Table		
	Frequency	**Percentage (%)**
Gender		
Female	162	53.6
Male	140	46.4
Total	302	100.0
Age (years)		
65-74	178	58.9
75-84	87	28.8
≥85	37	12.3
Total	302	100.0

When the diagnoses of 302 patients included in the study were examined, the diseases most frequently occurring were basal cell carcinoma (BCC) (17%), actinic keratosis (AK) (9%), seborrheic keratosis (SK) (8%), rosacea (6%), urticaria (4%), benign neoplasia (4%) (Table 2).

Table 2. Diagnoses		
Diagnosis		
	Frequency	**Percentage (%)**
Hyperpigmentation	4	1.3
Folliculitis	4	1.3
Rosacea	17	5.6
Perioral dermatitis	1	0.3
Cuperosity	3	1.0
Seborrheic dermatitis	12	4.0
Atopic dermatitis	1	0.3
Irritant contact dermatitis	11	3.6
Allergic contact dermatitis	7	2.3
Nummular dermatitis	4	1.3
Psoriasis	3	1.0
Lichen	4	1.3
Alopecia areata	1	0.3
Angioedema	1	0.3
Polymorphous light eruption	2	0.7
Lupus pernio	1	0.3
Tinea faciei	3	1.0
Herpes simplex	1	0.3
Herpes zoster	9	3.0
Verruca vulgaris	6	2.0
Lupus vulgaris	1	0.3
Discoid lupus erythematosus	3	1.0
Dermatomyositis	1	0.3
Lentigo simplex	7	2.3
Skin tag	3	1.0
Xanthelasma	3	1.0
Benign skin & appendages tumors	13	4.3
Melanocytic nevus	4	1.3
BCC	52	17.2
AK	27	8.9
Actinic cheilitis	5	1.7
Cutaneous horn	4	1.3
Keratoacanthoma	5	1.7
Venous lake	2	0.7
Pyogenic granuloma	1	0.3
Cicatrice	1	0.3
SK	26	8.6
Urticaria	13	4.3
Xerosis cutis	4	1.3
Squamous cell carcinoma	9	3.0
Angular cheilitis	1	0.3
Pemphigus vulgaris	10	3.3
Bullous pemphigoid	10	3.3
Kaposi sarcoma	2	0.7
Total	302	100.0

AK=Actinic keratosis, BCC=Basal cell carcinoma, SK=Seborrheic keratosis

Considering the lesion localizations of the patients, 35% of the lesions were in the malar region, 30% in the nose region, 26% in the forehead region, 12% in the neck region, 11% in the auricular region, 7% in the perioral region, 6% in the periorbital region, 5% in the mentum, 5% were on the lips, and 3% were on the eyebrows (Table 3).

Fifty-two patients were diagnosed with BCC. The age range of these patients was between 65-97, and the mean age was 76.1±7 years (mean ± SD). Forty-six per cent of patients were in the age range of 65-74 year; 33% were female and 67% male (Table 4,5). The affected sites were nose (56%), malar region (15%), auricular region (8%), perioral region (6%), forehead (6%), periorbital region (4%), eyebrows (4%), and mentum (2%) (Table 6).

Actinic keratosis was diagnosed in 27 patients. It was observed that the age range of these patients was between 65 and 96, and the mean age was 76.6±8.8 years (mean ± SD). Eighty-two per cent of patients were in the age range of 65-84 years; 52% were female while 48% were male (table 4,5). When the lesion localization of the patients was examined, it was observed that 59% had forehead, 26% had malar, 22% had nose and 4% had auricular area localization (Table 6).

Table 3. Lesion Localizations		
Localization		
Nose	Frequency	89
	Perc. (%)	29.5
Malar Region	Frequency	106
	Perc. (%)	35.1
Forehead	Frequency	78
	Perc. (%)	25.8
Mentum	Frequency	14
	Perc. (%)	4.6
Lips	Frequency	16
	Perc. (%)	5.3
Perioral Region	Frequency	20
	Perc. (%)	6.6
Periorbital Region	Frequency	19
	Perc. (%)	6.3
Eyebrows	Frequency	10
	Perc. (%)	3.3
Neck	Frequency	35
	Perc. (%)	11.6
Auricular and periauricular region	Frequency	32
	Perc. (%)	10.6
Perc.=Percentage		

There were 26 patients with SK in this study. When the demographic characteristics were examined, it was found that the age range was between 65 and 93, and the mean age is 73.5±8.1 years (mean ± SD). Sixty-nine per cent of the patients were in the age range of 65-74; 65% were female and 35% male (table 4,5). Fifty per cent of the lesions were located in the malar region, 35% on the forehead, 19% on the nose, 11% on and around the auricle, and 4% on the eyebrows (Table 6).

Seventeen patients were diagnosed with rosacea. Their age range is between 65-74, with a mean age of 68.3±3.12 years (mean ± SD). All patients were between 65-74 years of age; 53% of patients were female and 47% male (table 4,5). It was determined that 88% of the lesions were located in the malar region, 59% in the nasal region, 12% on the forehead and 12% in the mentum (Table 6).

Table 4. Age distribution of the most common diagnoses					
	Age				
Diagnoses	**Number of patients**	**Mean**	**SD**	**Min.**	**Max.**
BCC	52	76.08	7.87	65	97
AK	27	76.56	8.81	65	96
SK	26	73.5	8.15	65	93
Rosacea	17	68.3	3.12	65	74
AK=Actinic keratosis; BCC=Basal cell carcinoma; SK=Seborrheic keratosis; SD=Standard deviation; Min.=Minimum; Max=Maximum					

Table 5. Distribution of the most common diagnoses by gender and age groups									
	Gender	**female**	**male**	**TOTAL**	**Age**	**65-74**	**75-84**	**≥85**	**TOTAL**
BCC		32.7%	67.3	100%		46.2%	404%	13.5%	100%
AK		51.9%	48.1%	100%		40.7%	40.7%	18.5%	100%
SK		65.4%	346%	100%		69.2%	11.5%	19.2%	100%
Rosacea		52.9%	47.1%	100%		1000%	0%	0%	100%
AK=Actinic keratosis; BCC=Basal cell carcinoma; SK=Seborrheic keratosis									

Table 6. Most common lesion localizations of BCC, AK, SK and rosacea				
LOCATIONS	**BCC**	**AK**	**SK**	**ROSACEA**
Nose	55.8%	22.2%	19.2%	58.8%
Malar area	15.4%	25.9%	50.0%	88.2%
Forehead	5.8%	59.3%	34.6%	11.8%
Chin	1.9%	0%	0%	11.8%
Lips	0%	0%	0%	0%
Perioral area	5.8%	0%	0%	0%
Periorbital area	3.8%	0%	0%	0%
Eyebrows	3.8%	0%	3.8%	0%
Neck	0%	0%	0%	0%
Auricular and periauricular region	7.7%	3.7%	11.5%	0%
AK=Actinic keratosis; BCC=Basal cell carcinoma; SK=Seborrheic keratosis				

When the diagnoses of 302 patients included in the study were group concerning main dermatologic disease subgroups, it was observed that 22% were afflicted by erythematous-scaly diseases, 21% had cutaneous malignancy, 17.5% has benign neoplasms,

Table 7. Grouping of diagnoses		
	Freq.	**Perc. (%)**
Diagnoses		
Allergic/ Inflammatory Dermatoses	38	12.6
Dermatitis Group Diseases	37	12.3
Erythematous-Squamous Diseases	7	2.3
Infectious Diseases	20	6.6
Rheumatological Diseases	4	1.3
Bullous Diseases	20	6.6
Benign Neoplasms	53	17.5
Premalignant Changes	41	13.6
Malignancy	63	20.9
Melanocytic Lesions and Others	19	6.3
Total	302	100.0
Freq.= Frequency; Perc.=Percentage		

14% had premalignant changes, 13% had allergic/inflammatory dermatoses, 12% had dermatitis group diseases, 7% had cutaneous infections, 7% had autoimmune blistering disease, 6% had melanocytic lesions and miscellaneous, 1% had rheumatologic diseases (Table 7).

Disease diagnoses of the patients included in the study exhibited significant statistical differences according to gender (χ^2 = 31.531; p<0.05). Accordingly, 22% of 162 female patients were diagnosed with benign neoplasia, 17% with allergic/inflammatory dermatoses, 13% with cutaneous malignancy, and 12% with premalignant changes. When 140 male patients were examined, it was detected that 30% of them were diagnosed with cutaneous malignancy, 15% with premalignant changes, 14% with dermatitis group of diseases, and 12% with benign neoplasia (Table 8).

Table 8. The Relationship Between Disease Diagnoses and Gender						
Diagose groups		**Gender**		**TOTAL**	**χ^2**	**p**
		Female	**Male**			
Allergic/ Inflammatory Dermatoses	**Frequency**	27	11	38	5,299	,021*
	Percentage(%)	16,7	7,9	12,6		
Dermatitis Group Diseases	**Frequency**	17	20	37	1,004	,316
	Percentage(%)	10,5	14,3	12,3		
Erythematous-Squamous Diseases	**Frequency**	6	1	7	2,964	,085
	Percentage(%)	3,7	0,7	2,3		
Infectious Diseases	**Frequency**	6	14	20	4,814	,028*
	Percentage(%)	3,7	10,0	6,6		
Rheumatological Diseases	**Frequency**	3	1	4	0,744	,389
	Percentage(%)	1,9	0,7	1,3		
Bullous Diseases	**Frequency**	13	7	20	1,111	,292
	Percentage(%)	8,0	5,0	6,6		
Benign Neoplasms	**Frequency**	36	17	53	5,273	,022*
	Percentage(%)	22,2	12,1	17,5		
Premalignant Changes	**Frequency**	20	21	41	0,451	,502
	Percentage(%)	12,3	15,0	13,6		
Malignancy	**Frequency**	21	42	63	13,204	,000*
	Percentage(%)	13,0	30,0	20,9		
Melanocytic Lesions and Others	**Frequency**	13	6	19	1,781	,182
	Percentage(%)	8,0	4,3	6,3		
TOTAL		162	140	302	31,531	,000*
*p<0,005						

Pearson Chi-Square test was performed to determine whether the patients included in the study differed statistically according to gender in the disease groups. The most common diagnoses are malignancy, benign neoplasms, allergic/inflammatory dermatoses, and dermatitis group diseases. When the distribution of men and women in these disease groups was examined; It was observed that the diagnosis of malignancy and dermatitis group diseases was more common in men, while the diagnosis of benign neoplasms and allergic / inflammatory dermatoses were more common in women. Dermatitis group (χ^2 = 1.004; p>0.05), erythematous-scaly (χ^2 = 2.964; p>0.05), rheumatological (χ^2 = 0.744; p>0.05), bullous (χ^2 = 1.111; p> 0.05) diseases and premalignant changes (χ^2 = 0.451; p>0.05), melanocytic lesions and other (χ^2 = 1.781; p>0.05) diagnoses were not statistically different in terms of gender. Infectious skin diseases differed statistically significantly by gender and were more common in males (χ^2 = 4.814; p<0.05). Benign neoplasms were significantly by different concerning gender (χ^2 = 5.273; p<0.05) and were more common in women. The diagnosis of malignancy was statistically different according to gender and was more common in males (χ^2 = 13,204; p<0.05). The diagnosis of allergic/inflammatory dermatoses was statistically significant according to gender (χ^2 = 5.299; p<0.05) and was more common in females.

Considering the mean age of patients according to the disease group, the years were as follows: allergic/inflammatory dermatoses: 70.1±6.14 (mean ± SD)., dermatitis group of diseases: 74±7.5 (mean ± SD)., erythematous-squamous diseases: 69.6±5.22 (mean ± SD), cutaneous infections: 73.1±9.1 (mean ± SD), rheumatological diseases: 68±4.7 (mean ± SD), autoimmune bullous diseases: 72.8±8.2 (mean ± SD), benign neoplasms: 73.4±8.7 (mean ± SD), premalignant changes: 76.4±8.6 (mean ± SD), cutaneous malignancy: 76.5±7.6 (mean ± SD), melanocytic lesions and miscellaneous: 72±8.1 (mean ± SD). The highest mean age was found in patients with cutaneous malignancy, and those with the lowest mean age were the patients in the rheumatological diseases group (Table 9).

Table 9. The Relationship Between Disease Diagnoses and Age Groups

Diagose groups		Age (Years)			TOTAL	χ^2	p
		65-74	75-84	≥85			
Allergic/ Inflammatory Dermatoses	Frequency	32	4	2	38	11,486	,003*
	Percentage(%)	18,0	4,6	5,4	12,6		
Dermatitis Group Diseases	Frequency	19	16	2	37	5,075	,079
	Percentage(%)	10,7	18,4	5,4	12,3		
Erythematous-Squamous Diseases	Frequency	5	2	0	7	1,068	,586
	Percentage(%)	2,8	2,3	0,0	2,3		
Infectious Diseases	Frequency	14	2	4	20	4,124	,127
	Percentage(%)	7,9	2,3	10,8	6,6		
Rheumatological Diseases	Frequency	3	1	0	4	0,694	,707
	Percentage(%)	1,7	1,1	0,0	1,3		
Bullous Diseases	Frequency	14	3	3	20	1,994	,369
	Percentage(%)	7,9	3,4	8,1	6,6		
Benign Neoplasms	Frequency	34	11	8	53	2,167	,338
	Percentage(%)	19,1	12,6	21,6	17,5		
Premalignant Changes	Frequency	18	15	8	41	4,858	,088
	Percentage(%)	10,1	17,2	21,6	13,6		
Malignancy	Frequency	26	29	8	63	12,428	,002*
	Percentage(%)	14,6	33,3	21,6	20,9		
Melanocytic Lesions and Others	Frequency	13	4	2	19	0,782	,676
	Percentage(%)	7,3	4,6	5,4	6,3		
TOTAL		178	87	37	302	38,488	,003*

*p<0,005

Pearson Chi-Square test was performed to determine whether the disease diagnoses of the patients included in the study differed statistically according to categorized age groups. Dermatitis group diseases (χ^2 = 5.075; p>0.05), erythematous-squamous diseases (χ^2 = 1.068; p>0.05), infectious diseases (χ^2 = 4.124; p>0.05), rheumatological diseases (χ^2 = 0.694; p>0.05), bullous diseases (χ^2 = 1.994; p>0.05), benign neoplasms (χ^2 = 2.167; p>0.05), premalignant changes (χ^2 = 2.167; p>0.05) , melanocytic lesions and other (χ^2 = 0.782; p>0.05) diagnoses did not differ statistically significantly according to age groups. The status of having a diagnosis of malignancy was found to be statistically significant according to age groups (χ^2 = 12,428; p<0.05). It was observed that 41% of those diagnosed with malignancy were in the 65-74 age range, 46% were in the 75-84 age range, and 13% were 85 and over. The diagnosis of allergic/inflammatory dermatoses was statistically significant according to age groups (χ^2 = 11,486; p<0.05). It was determined that 84% of those diagnosed with allergic/inflammatory dermatoses were between the ages of 65-74, 10% were between the ages of 75-84, and 5% were 85 and over.

Disease diagnoses of patients included in the study had a significant statistical difference according to age (χ^2 = 38.488; p<0.05). When 178 patients between the ages of 65-74 were examined, 19% had benign neoplasia, 18% had allergic / inflammatory dermatoses, 15% had cutaneous malignancy. When 87 patients between the ages of 75-84 were examined, cutaneous malignancy was found in 33%, dermatitis group of diseases in 18%, premalignant changes in 17%, and benign neoplasia in 13%. When 37 patients aged 85 and over were assessed, it was detected that 22% had cutaneous malignancy, 22% had premalignant changes, and 11% had cutaneous infections (Table 9).

DISCUSSION

The increase in the geriatric population all over the world also increases the hospital admissions of these people. The skin of this population, like other systems, has its own characteristics such as fragility. Besides, polypharmacy can be a significant problem in these patients. For this reason, health assessments of these people require special knowledge and skills for the diseases (5). It is more urgent than ever to increase recognition of these diseases, determine their rates, and recognize the gender distributions. Furthermore, elderly individuals are more frequently involved in social and business environments today, can use social media actively, and therefore give more importance to their appearance (2). The face is one of the most remarkable factors in external appearance; therefore, attention to facial dermatoses and removal of disorders has increased. This situation may be related not only to aesthetic concerns, but also to health awareness. However, in this awareness, parameters such as education level, socioeconomic status, social support, and cognitive condition are also important (5).

Our study was based on the face and aging of the face. Earlier studies of this age group evaluated the whole body rather than focus regionally. In addition, there are studies in the literature that assess periorbital, malar, and periorificial dermatoses, but do not holistically consider the face (6). However, the face is the most important point especially in the person's appearance and is the striking region that reflects their expressions, and its lesions can be affected in a spectrum up to depression (7). We conducted this study because we think that this region, which is the most striking site of a person, should therefore be examined separately.

The geriatric population ages by two mechanisms: intrinsic (true) aging and photo aging. The increase in benign lesions such as SK and angiomas in the body, characteristic of intrinsic aging, has been mentioned in the literature. It has been stated that the facial localization of these SK lesions is also quite common (8,9). Our research similarly revealed an increase in the frequency of benign dermatoses of the facial region. It is noteworthy that after the age of 74, their frequency decreased with age. Increase in epidermal cellular heterogeneity and a decrease in the keratinocyte DNA repair mechanism, together with an age correlative decrease in Langerhans cells and melanocytes, are the physiopathological reasons for this true aging picture (10). Specifically, it is necessary to demonstrate with further studies whether the reason for the decrease in SC after the age of 74, which was determined in our study, is due to the decrease in hospital admissions, or whether they get used to that appearance after these ages and accept it as normal, or whether it is due to more serious health problems that the lesions are not prioritized. Besra et al. evaluated diseases located in the periorbital region and found that 25% of benign and malignant skin tumors detected in 250 patients increased to a high rate of 38.5% in our geriatric patients, and with whole facial location. Studies with a large series and evaluating these lesions on the whole face are required. The frequency of melanocytic lesions (6%) was compatible with nevoid events in our study (6).

However, Besra et al. examined not only the geriatric group, but all age groups. In addition, we understand a second reason for this increase is because the whole face was evaluated rather than periorbital localization. These findings were also compatible with photoaging, which is a second type of aging in the elderly. Increased sun exposure causes elastosis of the skin, irregular hyperpigmentation, hypopigmentation, and telangiectasias in addition to a series of benign and malignant neoplasms. Atrophy of the stratum corneum and a severe decrease in Langerhans cells are physiopathologically responsible for this (11).

In this study, it was observed that the distribution(s) between the disease diagnosis groups, genders, and age groups were different. While skin malignancies were at the forefront in older age groups, rheumatological diagnoses were found to be more common at younger ages. While the most common disease group in female patients is benign neoplasia (22%), malignancies take first place among males (30%). The rarest diseases in men are erythematous-squamous and rheumatological diseases with a rate of 0.7%. Rheumatological diseases are also the rarest for women (1.9%), followed by infectious and erythematous-squamous diseases (both 3.7%). To verify these data, multicenter epidemiological studies should be planned on a country-by-country basis around the world.

The most frequent facial skin diseases affecting patients over 65 years who visited our dermatology outpatient clinic were BCC (17%), AK (9%), SK (8%), rosacea (6%) and urticaria (4%) respectively. However, when the diseases were categorized, the most common disease groups were malignancies (21%), benign neoplasms (17.5%), premalignant changes (14%) and allergic/inflammatory dermatoses (13%). Malignancy, having the highest rate in this study, should be a warning for this group's healthcare providers, family physicians and, of course, dermatologists. Even if these lesions may not be the primary complaint of the patient in examinations, it is vital to screen these lesions on the face and make an early diagnosis. In other words, in elderly patients who present with dermatological complaints on the face or anywhere else, it is necessary to be more careful in terms of malignancies and dermoscopy should be used. It is also important that these lesions may need to be addressed more carefully in male patients because the frequency is higher in this gender. Thus, both mortality and morbidity will be reduced. In fact, we advise trainings to primary care family physicians, establishing patient schools for the geriatric population with good cognition, and educating caregivers.

Garcovich et al. emphasized that BCC occupies 80% of all skin cancers in the Caucasian population, and the frequency is increasing, especially in the population over 65 years old (12). It has been stated in the literature that BCC is most commonly located on the face (13). In our study, BCC was the facial dermatosis with the highest prevalence compared to other facial lesions (17.2%). Oda et al. screened geriatric BCC and determined that the most common localization in the face was the cheeks, followed by the nasal, periorbital, frontal and labial areas(13). In our study, the most common localization was the nose, followed by the malar region and the ear, respectively. There are different data on localizations all over the world. In addition, another importance of lesion localization for BCC is that it can change the treatment approach and prognosis (14). It is known that lesion localization in BCC may be related to the angle of UV lights (15). This therefore makes it likely to find variations between countries (16). In this context, the determination of BCC localizations according to latitude and longitudinal location characteristics may be important for BCC, which may require more aggressive treatment strategies in some localizations.

One of the most important contributions of this study is to obtain data on facial dermatoses in the geriatric age group in Turkey, also to the world literature epidemiologically. Thus, the formation of multi-center working groups can be encouraged. It is known that professions and hobbies have a significant effect on skin lesions, especially on visible body areas (17,18). Furthermore, when we review reports from around the world, it has been determined that dermatoses in this population are a frequent research topic, but diseases of the facial skin are neglected. Considering the increasing elderly population all over the world, we consider it important to disclose epidemiological data on all other organ diseases and, indeed, dermatological diseases of geriatric patients. With data gathered from more precisely focused medical studies, diagnostic and therapeutic approaches to more frequent and life-threatening diseases can continue accelerated development.

It is known that professions and hobbies have also an essential effect on skin lesions, especially on visible body areas. One of the limitations of this study is that the occupations or hobbies of these patients throughout their lives were not known or evaluated. In addition, the height and weight of patients could not be obtained due to retrospective data, and facial dermatoses that may be associated with weight could not be evaluated. In addition, skin type, genetic background and ethnic origin of

the patients could not be evaluated in this study. There is a need for large series studies evaluating these data together. Besides, although we do not have any data comparing the time period before COVID-19 pandemics, the patient numbers may be decreased due to the fear of hospital admissions. This hypothesis should be verified with further studies.

CONCLUSION

In older ages, which is a special and fragile period such as the newborn period, the patient's contact with environmental stimuli is minimized, and are more standardized. By including this group in our study, we compared the cross-sectional results of this feature that we will obtain from our country and the literature data, which we consider as a similar group. Our results were consistent with the literature. We think that it will make a great contribution to the literature by observing a large patient group in the elderly, a group with high doctor dependence, in which all dermatoses in the face are questioned. We think that new studies comparing age groups statistically will contribute to the identification of unmet needs in this regard.

DISCLOSURES

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Ophthalmology / Göz Hastalıkları

Alterations of Neuroretinal and Corneal Thickness in Hashimoto's Thyroiditis

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ABSTRACT

Purpose: To compare changes in macula, retinal nerve fiber layer (RNFL) and central corneal thickness (CCT) in patients with Hashimoto's thyroiditis (HT) with age-matched healthy control group.

Materials and Methods: This study was conducted with a prospective, observational, cross-sectional design. The individuals participating in the study were divided into 2 groups: patients with a diagnosis of HT (group 1, n:54 eyes) and age-matched healthy participants (group 2, n:70 eyes). Corneal, retinal and macular thickness measured by optical coherence tomography. Mean outcome measurements were CCT, intra-ocular pressure (IOP), central 1 mm foveal thickness (CFT), subfoveal choroidal thickness (SFCT), total macular volume (TMV), central 1 mm foveal volume (CFV), and RNFL thickness in superior, nasal, inferior and temporal quadrants.

Results: The mean IOP was 17.07±2.34µm in group 1 and 14.20±2.76µm in group 2, respectively (p<0.001). Mean CCTs were 539.44±35.27µm and 555.06±40.53µm (p=0.001), CFTs were 227.35±17.52µm and 230.38±23.52µm (p=0.57), SFCT were 210,79±20,13µm and 268,47±24,56µm (p<0.001), TMVs were 7.16±0.35mm3 and 7.02±0.26mm3(p=0.07), CFVs were 0.17±0.01mm3 and 0.19±0.07mm3 (p=0.16) in group 1and group 2, respectively. RNFL thickness values were significantly thinner in the group 1(p<0.05) in all quadrants except for the nasal quadrant (p=0.086).

Conclusion: Hypothyroidism secondary to HT may be a determining factor affecting the development of the cornea and retina. Elevated IOP and decrement of RNFL thickness in children with HT increased the risk of developing glaucoma, as well as decreased SFCT may predispose to the development of chorioretinal disorders in the future.

Keywords: Corneal thickness, Hashimoto's thyroiditis, retinal nerve fiber layer thickness, macula

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Hashimoto Tiroiditinde Nöroretinal ve Kornea Kalınlığındaki Değişiklikler

ÖZET

Amaç: Hashimoto tiroiditi (HT) olan hastalarda makula, retina sinir lifi tabakası (RSLT) ve santral kornea kalınlığındaki (SKK) değişiklikleri yaşa uygun sağlıklı kontrol grubu ile karşılaştırmak.

Hastalar ve Yöntemler: Bu çalışma prospektif, gözlemsel, kesitsel dizayn ile yapılmıştır. Çalışmaya katılan bireyler 2 gruba ayrıldı: HT tanısı olan hastalar (grup 1, n: 54 göz) ve yaşları eşleştirilmiş sağlıklı katılımcılar (grup 2, n: 70 göz). Optik koherens tomografi (OKT) ile kornea, retina ve maküler kalınlıklar ölçüldü. Ortalama sonuç ölçümleri SKK, göz içi basıncı (GİB), merkezi 1 mm foveal kalınlık (MFK), subfoveal koroid kalınlığı (SFKK), toplam maküler hacim (TMH), santral 1 mm foveal hacim (SFH) ve üst, nazal, alt ve temporal kadranlardı.

Bulgular: Ortalama GİB grup 1'de 17.07 ± 2.34µm, grup 2'de 14.20 ± 2.76µm idi (p <0.001). Ortalama SKK'lar 539.44 ± 35.27µm ve 555.06 ± 40.53µm (p = 0.001), SFK'lar 227.35 ± 17.52µm ve 230.38 ± 23.52µm (p = 0.57), SFKK 210,79 ± 20,13µm ve 268,47 ± 24,56µm idi Grup 1 ve grup 2'de sırasıyla, (p <0.001), TMH'lar 7.16 ± 0.35mm3 ve 7.02 ± 0.26mm3 (p = 0.07), CFV'ler 0.17 ± 0.01mm3 ve 0.19 ± 0.07mm3 (p = 0.16) idi. Grup 1'de RSLT kalınlık değerleri, nazal kadran hariç tüm kadranlarda anlamlı olarak daha ince bulundu (p <0.05) (p = 0.086).

Sonuç: HT'ye bağlı hipotiroidizm, kornea ve retinanın gelişimini etkileyen belirleyici bir faktör olabilir. HT'li çocuklarda yüksek GİB ve RSLT kalınlığının azalması, glokom gelişme riskini artırdığı gibi, azalmış SFKK de gelecekte korioretinal bozuklukların gelişimine yatkınlık yaratabilir.

Anahtar Kelimeler: Kornea kalınlığı, Hashimoto tiroiditi, retina sinir lifi tabakası, makula

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Hashimoto's thyroiditis (HT) was firstly described by Hakaru Hashimoto in 1912 which had explained by pathological mechanism as: the thyroid gland is attacked by antibody-mediated immune processes (1). Thyroid function varies from euthyroidism to thyrotoxicosis. With the development of hypothyroidism in patients, the enlarged thyroid gland generally undergoes atrophy (2). No information on the pathogenesis of HT was known until 1956. Rose et al. have reported thyroglobulin antibodies and thyroiditis in rabbits which immunized with thyroid extract (3). Thyroid hormone (TH) plays a critical role in eye embryogenesis, but its effect on the development of cornea and neuroretinal tissue is not fully understood. TH can cause a wide variety of effects on different neural tissues, including proliferation, differentiation, and migration (4). There are several studies in the literature with conflicting results investigating the relationship between hypothyroidism and retino-choroidal or corneal changes, as well as ocular alterations (5-7). Herein, we aimed to investigate macular thickness, subfoveal choroidal thickness (SFCT), central corneal thickness (CCT), and retinal nerve fiber layer (RNFL) thickness in the patients with the diagnosis of hypothyroidism due to HT and compare the results with healthy age-matched control group.

MATERIALS AND METHODS

This prospective, single-center clinical study was conducted in the ophthalmology clinic of a tertiary hospital in collaboration with the endocrinology clinic between January 2015 and February 2018. The study conformed to the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee. Informed written consent was obtained from each participant. Patients with any sign of orbitopathy, corneal pathology, glaucoma, and retinal vascular disease such as diabetic or hypertensive retinopathy were excluded from the study. The patients who had the diagnosis of hypothyroidism due to HT in the outpatient clinic of the endocrinology department were enrolled as study group. Healthy age-matched participants constituted as the control group. Individuals with HT are in remission and under strict monitoring. A complete ophthalmic examination including visual acuity with Snellen chart, intraocular pressure measurement (IOP) (Goldmann applanation), anterior segment and fundus examinations, measurements of corneal, macular, SFCT and RNFL thickness were performed for each patient. CCT measurements were implemented by optical coherence tomography (OCT) (Optovue Avanti®). The mean of three sequential measurements from the central cornea was utilized for the assessment. RNFL thickness were measured by spectral domain optical coherence tomography (SD-OCT) (Optovue Avanti® Inc., Fremont, CA, USA). The SD-OCT assessments were performed in a dim room after mydriasis with tropicamide 0.5% drops by one of the authors (OOO). Mean outcome measures were central foveal thickness (CFT), mean SFCT, total macular volume (TMV), central foveal volume (CFV), and the RNFL thickness in the superior, nasal, inferior and temporal quadrants calculated automatically by SD-OCT. Subfoveal choroidal thickness were measured by the enhanced depth image optical coherence tomography (EDI-OCT) imaging method described by Spaide et al (8). SFCT was characterized as the vertical distance from the basal edge of retinal pigment epithelium below the central fovea to the endpoint of the choroid-scleral junction. Figure 1 shows EDI-OCT and mapping of the macula measurements on eyes with HT. Figure 2 shows optic nerve head measurements from an healthy individual. Figure 3 demonstrates the CCT measurement of a healthy individual.

Statistical analysis

The data was analyzed by using the Statistical Package for Social Science (SPSS) programme (SPSS version 15.0 for Windows; SPSS, Chicago, IL). Levene test for equality of variances and t test for equality of means were used for the comparison of the groups. P value of < 0.05 was considered as statistically significant.

RESULTS

Twenty-seven participants with 54 eyes that female:male ratio was 12:15 in group 1 and 35 participants with 70 eyes that female:male ratio was 16:19 in group 2 were included in study. There was no statistically significant difference in demographic data between the groups ($p > 0.05$). The mean age was 12.4±1.3 years (range, 9-14 years) in group 1, and 11.9±1.4 years (range, 7-14 years) in group 2. The mean weight and height were 36.9±8.4 kg and 146.3±15.2 cm in group 1; 37.7±7.6 kg and 147.4±13.9 cm in group 2. Descriptive characteristics (age, weight, height, gender distribution) of each groups are shown in Table 1. The mean CCT was 539.44 ± 35.27 µm in group 1 and 555.06 ± 40.53 µm in group 2 ($p=0.001$). The mean IOP was 17.07 ± 2.34 µm in group 1 and 14.20 ± 2.76 µm in group 2 ($p<0.001$). The mean CFT was 227.35±17.52 µm in group 1, 230.38±23.52 µm group 2 ($p=0.001$). Mean SFCT was 210.79±20.13 µm in group 1, 268.47±24.56 µm group 2 ($p<0.001$). Mean TMVs were 7.16±0.35 mm3 and 7.02±0.26 mm3($p=0.07$), CFVs were 0.17±0.01 mm3 and 0.19±0.07 mm3 in group 1 and group 2, respectively ($p=0.16$).

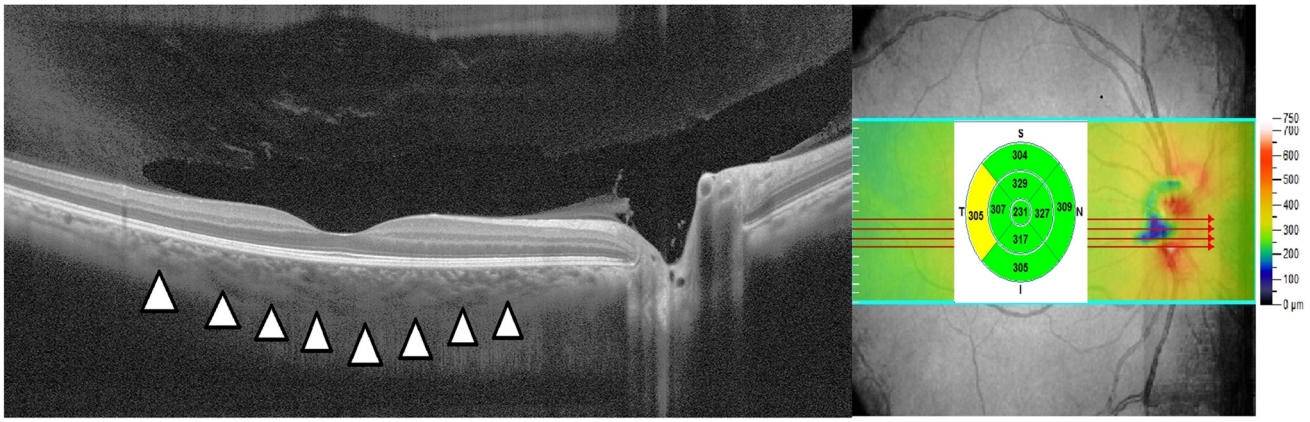

Figure 1. Enhanced optical coherence tomography (EDI-OCT) and mapping of the macula in eyes with Hashimoto's thyroiditis are shown. White arrows show the choroidal-scleral junction and its border.

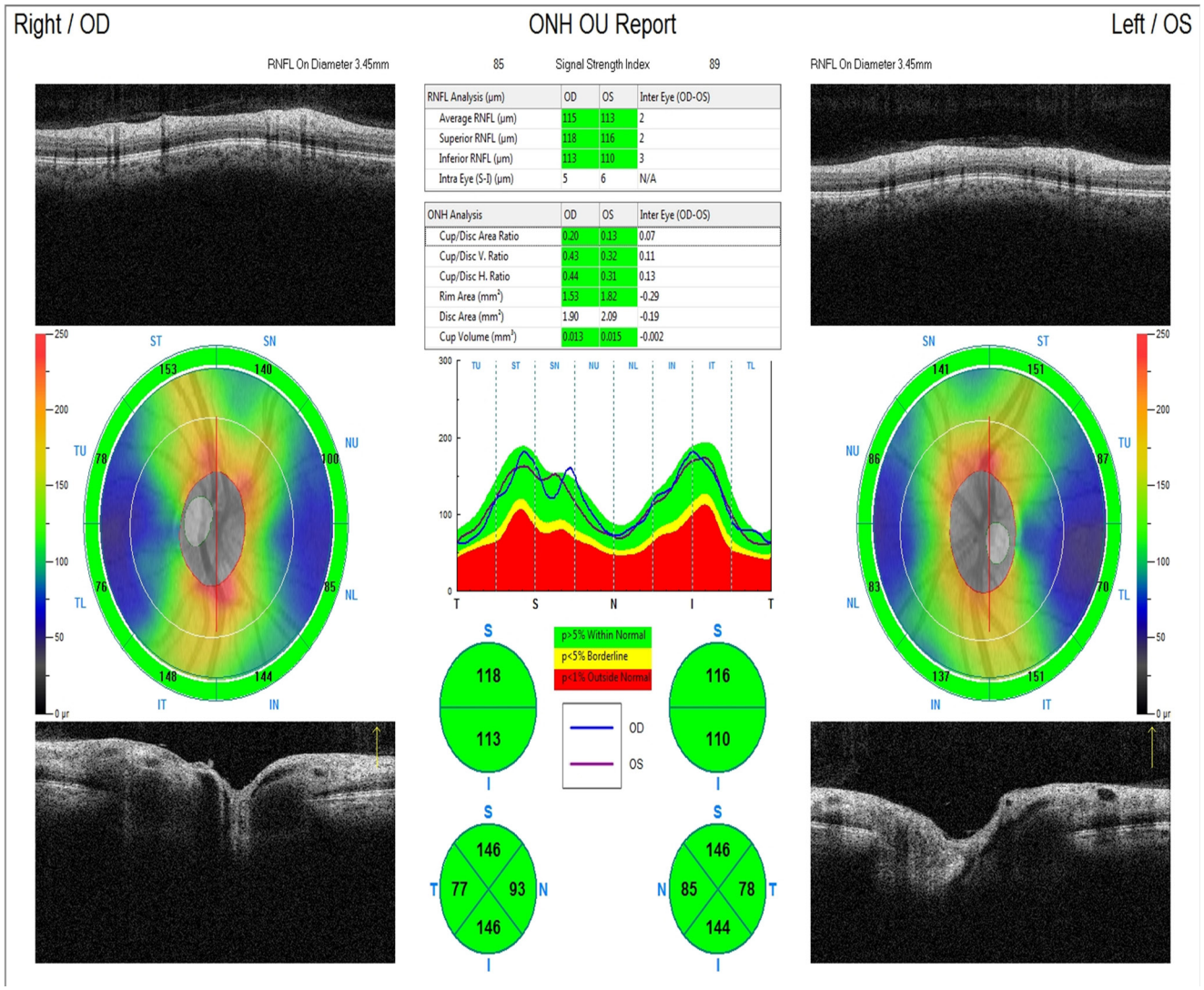

Figure 2. The optic nerve head (ONH) measurements of a healthy individual are shown.

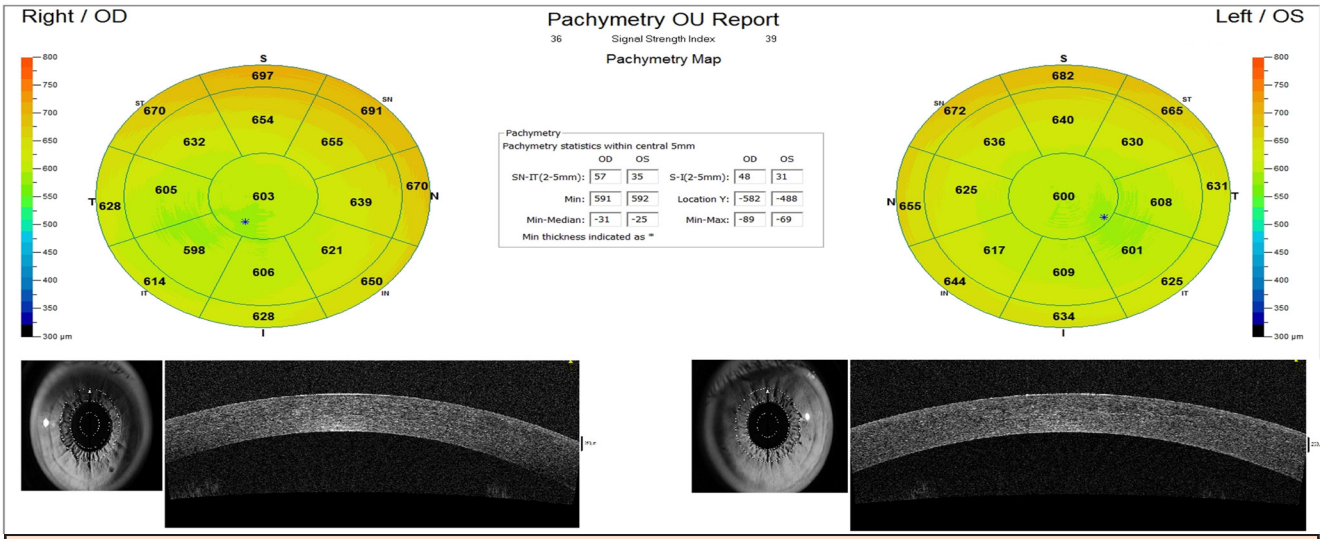

Figure 3. The image of central corneal thickness (CCT) measurement of a healthy individual was displayed.

Table 1: Demographic characteristics of groups

Mean ±SD	Group 1 Hashimoto group (n=54)	Group 2 Control Group (n=70)	*p values*
Age (years)	12.4±1.3 (9-14 years)	11.9±1.4 (7-14 years)	***0.879***
Weight (kg)	36.9±8.4	37.7±7.6	***0.745***
Height (cm)	146.3±15.2	147.4±13.9	***0.912***
Male/Female (n)	15/12	19/16	***0.749***

Student t test*
n:number; SD, standard deviation.

Table 2. Results of the study

Mean ± SD	Group 1 Hashimoto Group (n=54)	Group 2 Control Group (n=70)	*p values*
CFT, µm	227.35±17.52	230.38±23.52	***0.57***
SFCT, µm	210.79±20.13	268.47±24.56	***0.001****
TMV, mm3	7.16±0.35	7.02±0.26	***0.07***
CFV, mm3	0.17±0.01	0.19±0.07	***0.16***
IOP, mmHg	17.07 ± 2.34	14.20 ± 2.76	***0.002****
CCT, µm	539.44 ± 35.27	555.06 ± 40.53	***0.001****

Student t test*
CFT: Central 1 mm foveal thickness,
SFCT: Subfoveal choroidal thickness at the foveal pit,
IOP: Intraocular pressure, CCT: Central corneal thickness.
n: number; SD, standard deviation.

The results of the study are summarized in Table 2. As for RNFL measurements, mean RNFL thicknesses in central, superior, inferior, nasal and temporal quadrants were 109.40±12.50 µm, 130.72±16.38 µm, 139.42±17.60 µm, 81.14±9.51 µm, and 72.18±8.08 µm in group 1, and 115.41±12.80 µm, 141.65±17.48 µm, 156.25±17.96 µm, 80.67±11.84 µm, and 76.81±12.43 µm in group 2 (p=0.019, p=0.048, p=0.014, p=0.86 and p=0.028). RNFL thickness analysis of the study are given in Table 3. Figure 4 shows graphic of the results in the study.

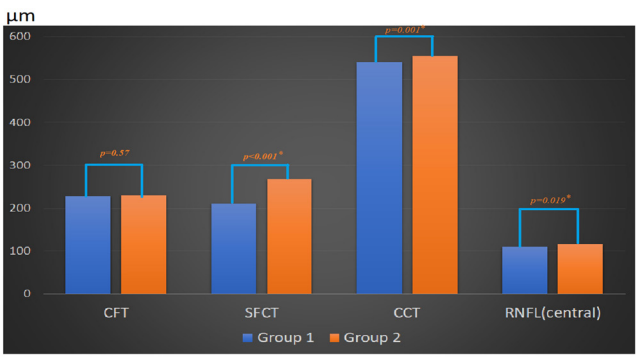

Figure 4. The graphic of the results is summarized in the study.

Table 3. Retinal nerve fiber layers analysis of the study			
Mean ± SD	**Group 1 Hashimoto Group (n=54)**	**Group 2 Control Group (n=70)**	***p values***
Mean RNFL central, µm	109.40 ± 12.50	115.41 ± 12.80	***0.019****
Mean RNFL superior, µm	130.72±16.38	141.65±17.48	***0.048****
Mean RNFL inferior, µm	139.42±17.60	156.25±17.96	***0.014****
Mean RNFL	81.14±9.51	80.67±11.84	***0.86***
nasal, µm	72.18±8.08	76.81±12.43	***0.028****
Mean temporal RNFL, µm			

DISCUSSION

Hypothyroidism is second common endocrine disorder following diabetes mellitus (9). HT is also known as chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis, and lymphadenoid goiter. Most patients with HT are euthyroid or have subclinical hypothyroidism with goiter and circulating thyroid antibodies. As time passes, overt hypothyroidism will develop at a rate of about 5% per year (2). The specific factor initiating autoimmunity to thyroid antigens is a dilemma. Similar to other autoimmune diseases, HT is assumed to appear from a breakdown of self-tolerance to thyroid antigens (10). Latest studies have focused attention on many contributor to the increased risk such as; vitamin D receptor gene polymorphisms (11), interleukin 6 gene promoter polymorphism (12), polymorphism in the interferon gamma gene (13), T cell receptor restriction fragment length polymorphism (14), specific allotypes of the immunoglobulin G heavy chain (15), CT 60 polymorphism of cytotoxic T-lymphocyte-associated protein-4 maps (16), and X chromosome inactivation (17). Thyroid hormone is crucial for the normal development of the central nervous system (18). Clinical and experimental studies have focused attention on the role played by TH also in neuroretinal development. However, knowledge on TH mechanisms on the developing visual system is still uncompleted. Recently, many studies have demonstrated the implication of TH in cone differentiation during the retinal development, growth and regeneration (19). Visual system morphogenesis and functioning rely on the accurate location of specific cells and the formation of relevant intercellular connections (20,21). Pinazo-Duran et al. investigated the role of TH in the developing retina and optic nerve, in a rat model of controlled TH deficiency. They reported that a depletion in the volume of the eye ($p<0.001$) and optic nerve cross- sectional zone ($p<0.001$), attenuation of the retinal layers ($p<0.001$), and remarkably postponed glial development and myelination in the TH defiency optic nerves ($p<0.001$), as compared to controls (22). Durieux et al. investigated electroretinogram (ERG) findings in three hypothyroid adult dogs with and without levothyroxine treatment, and reported that a dose of 20 µg/kg of levothyroxine given to adult dogs was associated with a noticeable peak time shortening of both photopic and scotopic ERGs (23). Ittermann et al. used data from 3189 individuals and investigated association between serum thyrotropin (TSH) levels and retinal artery narrowing and defined by arterio-venous ratio from static vessel analysis. They reported that high serum TSH levels were accompanied by retinal arteriolar narrowing, and described potential mechanisms by long-term hypertension, atherosclerotic processes, and inflammation (24). Studies about the effects of thyroid disorders on central corneal thickness are still unsatisfactory. The implication of TH in corneal physiology is being investigated in some studies. Conrad et al. reported the presence of thyroxin receptors alpha and beta in the chicken cornea (25). Bahceci et al. demonstrated a significant increase in CCT in hypothyroid patients that could be reversed with thyroxine replacement medication. Additionally, they concluded that the prevalence of glaucoma in hypothyroidism might not be as high as they previously reported when IOP was corrected for CCT (26). In the study of Gül et al., it was aimed to compare choroidal thickness in active and stable phases of Hashimoto thyroid eye disease. Subfoveal, temporal macula, nasal macula, temporal peripapillary and nasal peripapillary choroidal thickness measurements were performed in 23 eyes of 23 patients. SFCT was significantly thicker in the group with thyroid eye disease in the active phase than in the group with stable phase disease ($p=0.04$) (6). In our study, CCT was thicker in patients with HT, and found to be statistically significant difference in CCT among the groups ($p=0.001$).

Although similar results were obtained in our study, the sample size and prospective design constituted our superior aspects compared to this study. association between hypothyroidism and open angle glaucoma but none of them evaluate The literature contains controversial results considering the d patients according to etiology. Some studies report an association, whereas others failed to find such an association (27-29). Lin et al. investigated the risk of open-angle glaucoma after a diagnosis of hypothyroidism during the 5-year follow-up period. Their study group consisted of 257 hypothyroidism patients and the comparison group involved 2056 subjects. They reported that hypothyroidism patients had 1.78-fold greater risk of developing open angle glaucoma. In our study, IOP was higher in patients with HT, and there was statistically significant difference in IOP between the groups (p=0.002) (30). In a study conducted by Kırgız et al., they compared CCT and IOP values of 48 HT and 49 control healthy eyes. Although there was no significant difference in central corneal thickness (CCT) values between the HT group and the control group (p = 0.65), IOP values were significantly higher in HT group (p = 0.001) (7). To the best of our knowledge, this study is the first of its kind where individuals with HT were examined for corneal and neuroretinal thicknesses together. Bahceci et al. measured RNFL thicknesses parameters with scanning laser polarimeter and did not find any statistically significant result formed by hypothyroidism (26). Ozturk et al. investigated RNFL thickness of 33 patients diagnosed to have primary hypothyroidism and reported statistically significant change ($p<0.05$) (31). A statistically significant change was found in mean RNFL thickness among the groups in our study ($p<0.05$). Limitations of this study are the small sample size, lack of control group and short follow-up period that might affect the statistical power. Advantages of present study are prospective design and detailed statistical parameters. In conclusion, hypothyroidism due to HT may be definitive factor affecting corneal and retinal development as presumed in some previous studies. Therefore, close follow-up and frequent examinations should be prioritized. Future prospective studies involving large subsets may provide further evidence of the susceptibility of HT to ocular disease.

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Informed consent: Informed consent was obtained prior to every surgical procedure from all individual participants included in the study.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Ophthalmology / Göz Hastalıkları

Generic Cyclosporine in the Treatment of Dry Eye Disease

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ABSTRACT

Objectives: To investigate the efficacy and safety of a generic Cyclosporine 0.05% ophthalmic emulsion in chronic dry eye disease.

Materails and Methods: Thirty patients with dry eye disease were included in this observational, prospective study. Patients were examined at baseline, at month -1,-3 and 6 of the study. The following were evaluated at each visit: CDVA (corrected distance visual acuity), corneal and conjunctival staining (Oxford) score, TBUT (tear break-up time), Schirmer-2 score, OSDI (Ocular Surface Disease Index) score, patient's subjective rating scale of ocular discomfort, daily use of concomittant artificial tears, the researcher's assessment of the global treatment response, and IOP (intraocular pressure). In addition, drug-related side effects were evaluated individually in each examination. When initiating dry eye treatment, cyclosporine was combined with topical loteprednol etabonate 0.5%.

Results: There was a statistically significant improvement from baseline in corneal and conjunctival staining (decrease in mean Oxford score), TBUT, Schirmer-2 values, OSDI score, patient's subjective rating score for ocular discomfort, and mean physician's subjective assessment of global response to treatment at all follow-up visits ($p<0.001$). The mean daily use of artifical drops decreased statistically at all time points (<0.001). The most commonly reported adverse events were ocular burning (6.7%), followed by stinging (3.3%), conjunctival hyperemia (3.3%), foreign body sensation (3.3%), and visual disturbance (3.3%).

Conclusion: Generic cyclosporine 0.05% ophthalmic emulsion with loteprednol etabonate 0.5% on initiation treatment has well-tolerability and improves subjective and objective measures of dry eye disease.

Keywords: Dry eye syndromes, cyclosporine, generic equivalency

Kuru Göz Hastalığının Tedavisinde Jenerik Siklosporin

ÖZET

Amaç: Jenerik %0.05 siklosporin oftalmik emülsiyonunun kronik kuru göz hastalığındaki etkinliğini ve güvenliğini araştırmak.

Gereç ve Yöntem: Kuru göz hastalığı olan 30 hasta, bu gözlemsel prospektif çalışmaya dahil edildi. Hastalar başlangıçta, çalışmanın 1., 3. ve 6. ayında değerlendirildi. Çalışmada değerlendirilen parametreler şunlardı: DUGK (düzeltilmiş uzak görme keskinliği), korneal ve konjonktival boyanma (Oxford) skoru, GKZ (gözyaşı kırılma zamanı), Schirmer-2 skoru, OSDI (oküler yüzey hastalık indeksi) skoru, GİB (göziçi basıncı), günlük suni gözyaşı kullanım miktarı, araştırmacının global tedavi cevabını değerlendirmesi ve oküler rahatsızlık için hastanın subjektif değerlendirme skoru. Ayrıca, her muayenede ilaçla ilişkili yan etkiler değerlendirildi. Kuru göz tedavisinin başlangıcında, siklosporinle birlikte topikal %05 loteprednol etabonat kombine edildi.

Bulgular: Korneal ve konjonktival boyanma, GKZ, Schirmer-2 değerleri, OSDI skoru, hastanın subjektif değerlendirme skoru ve araştırmacının global tedavi cevabını değerlendirmesi; başlangıç seviyesine kıyasla her vizitte düzelmiş olarak bulundu ($p<0.001$). Her vizitte, günlük suni gözyaşı kullanımı da düşmüş olarak bulundu ($p<0.001$). En sık bildirilen ilaçla ilişkili yan etkiler; oküler yanma (%6.7), batma (%3.3), konjonktival hiperemi (%3.3), yabancı cisim hissi (%3.3), ve görme bozukluğu (%3.3) idi.

Sonuç: Başlangıç tedavisinde %0.5 loteprednol etabonat ile kombinlenmiş jenerik %0.05 siklosporin oftalmik emülsiyonu, iyi tolere edilmekte ve kuru gözün subjektif ve objektif ölçeklerini iyileştirmektedir.

Anahtar Kelimeler: Kuru göz sendromları, siklosporin, jenerik eşdeğerlik

"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensorial abnormalities play etiological roles" as defined by Tear Film and Ocular Surface Society Dry Eye Workshop 2 Study Group (1).

Tear replacement with ocular lubricants or artificial tears is the mainstay of dry eye diseease (DED) treatment. However, these products do not target the underlying pathophysiology of DED and the symptomatic relief they provide is temporary. Desiccating stress can induce ocular surface damage and generate innate and adaptive immune responses. These inflammatory cascades lead to further ocular surface damage and the development of a self-perpetuating inflammatory cycle (2).

Cyclosporine is an immunomodulatory drug with anti-inflammatory properties, as well as other properties to manage DED (3-5). Cyclosporine inhibits IL-2 activation of lymphocytes (5). Treatment with cyclosporine reduces many markers of inflammation (6,7) and also reduces elevated tear osmolarity (8). Cyclosporine also has anti-apoptotic effects establishing the normal epithelial cell/leukocyte relationship in DED (9,10). Additionally, cyclosporine treatment results in recovery of reduced goblet cell density in the conjunctiva of subjects with DED (11,12).

The first topical cyclosporine A commercially available in 2000 was Restasis (Cyclosporine A 0.05%, Allergan, USA). Restasis was approved by the FDA for the treatment of moderate-to-severe DED in 2003, based on an improvement in tear production measured by the Schirmer test in 15% of patients, compared to 5% of vehicle-treated controls (2). Depores (cyclosporine 0.05%, Deva Pharmaceuticals, Turkey) is a generic cyclosporine 0.05% ophthalmic emulsion which became commercially available in Turkey in 2013. In this study, we evaluated the efficacy and safety of this generic CsA 0.05% in chronic dry eye patients.

MATERIAL AND METHODS

Thirty patients with dry eye disease were included in this observational, prospective study. The study was performed according to the guidelines of the Helsinki Declaration and approved by the institutional ethics committee (Acibadem Mehmet Ali Aydinlar University Medical Research Ethics Committee, 14.01.2016, 2016/1). Informed consent was given by all patients. The inclusion criteria were age >18 years and symptomatic dry eye disease in which artificial tears and gels were not sufficient. Exclusion criteria were use of systemic or topical CsA in the previous 90 days, women who were pregnant/planning a pregnancy or lactating, active ocular infections and suspected hypersensitivity to any of the ingredients in the CsA formulation.

Patients were examined at baseline, at month -1, -3 and -6 of treatment. The following were evaluated at each visit: CDVA (corrected distance visual acuity), *corneal and conjunctival fluorescein staining* (Oxford) score, *tear break-up time, Schirmer score, OSDI* (Ocular Surface Disease Index) score, *IOP* (intraocular pressure, by air-puff tonometry), and *daily use of concomittant artificial tears*, the *researcher's assessment of the global treatment response* (0: full recovery, 1: 90% improvement, 2: 75% improvement, 4: 25% improvement, 5: no change, 6: worsening), *patient's subjective rating scale* (0 to 4) of ocular discomfort (stinging/burning, itching, sandiness/grittiness, blurred vision, light sensitivity, pain or soreness). In addition, drug-related side effects were evaluated individually in each examination: Burning, stinging, conjunctival hyperemia, foreign body sensation, blurred vision, eye pain, and other if any.

When initiating dry eye treatment, cyclosporine A was combined with loteprednol etabonate. Patients received topical CsA %0.05 (Depores, Deva Pharmaceuticals, Turkey) twice daily and artificial tears (sodium hyaluronate) as needed. Topical loteprednol 0.5% (Lotemax, Bausch and Lomb, USA) was given for 4 weeks, started as QID for the first 2 weeks and BID for the following 2 weeks. Compliance with the treatment regimen was assessed by patient interview at each visit.

Only the data from the "worse" eye were included in the analyses for efficacy variables. The "worse" eye was defined as the eye with the worse Schirmer (with anesthesia) value and the worse sum of corneal and conjunctival staining. If both eyes are similar, then the right eye was used. The "worse" eye was identified at baseline measurements, and data from this eye were used for all subsequent analyses. However, all safety analyses included data from both eyes.

IBM SPSS Statistics 25.0 statistical software (IBM, USA) was used for statistical analysis. Normality of difference scores for three or more observations was assessed using skewness and kurtosis statistics. Descriptive statistics

(arithmetic mean±standard error) and repeated measures of analysis of variance were used for statistical analyses. A p value of less than 0.05 was considered as statistically significant.

RESULTS

Of the thirty patients, 22 (73.3%) were females and 8 (26.7%) were males. The average age was 47.3 ± 1.4 (34-64) years. The clinical findings of the patients are summarized in Table 1.

Corneal and Conjunctival Staining

At baseline, the mean Oxford score for corneal staining was 2.6±0.11 (1-4). There was a statistically significant improvement from baseline in corneal staining (decrease in mean Oxford score) at all follow-up visits (p<0.001).

At baseline, the mean Oxford score for nasal interpalpebral conjunctival staining was 2.3±0.14 (1-4). There was a statistically significant improvement from baseline in nasal interpalpebral conjunctival staining (decrease in mean Oxford score) at all follow-up visits (p<0.001).

At baseline, the mean Oxford score for temporal interpalpebral conjunctival staining was 1.9±0.11 (1-3). There was a statistically significant improvement from baseline in temporal interpalpebral conjunctival staining (decrease in mean Oxford score) at al follow-up visits (p<0.001).

Tear Break Up Time (TBUT)

At baseline, the mean TBUT was 3.7±0.3 (1-9). There was a statistically significant improvement from baseline in TBUT at all follow-up visits (p<0.001).

Schirmer Tear Test

At baseline, the mean Schirmer values (obtained with anesthesia) was 6.0±0.4. There was a statistically significant improvement from baseline in Schirmer values at all follow-up visits (p<0.001).

OSDI Score

The OSDI score, evaluating the impact of patient's dry eye disease on vision-related functioning, was 40.6±1.9 (22.9-38.5) at baseline, 23.0±1.4 (12.5-45.8) at month 1, 15.3±1.4 (12.5-45.8) at month 3 and 8,0±0.8 (1.5-18.7) at month 6. The improvement in OSDI score was statistically significant at all time points (p<0.001).

Patient's Subjective Rating Scale

The mean patient's subjective rating score for ocular discomfort (stinging/burning, itching, sandiness/grittiness, blurred vision, light sensitivity, pain or soreness) was 2.2±0.15 (1-4) at baseline. Statistically significant changes from baseline were observed at all time points in patient's subjective rating scale (p<0.001).

Daily Use of Concomitant Artificial Tears

The mean daily use of artifical drops was 5.5±0.29 (3-9) at baseline, 2.8±0.19 (1-5) at month 1, 1.8±0.12 (0-2) at month 3 and 1.0±0.12 (0-2) at month 6. There were statistically significant decreases in the frequency of artificial tear use at all time points (p<0.001).

Table 1. Summary of the Clinical Data of the Study

	Baseline	Post-treatment month 1	Post-treatment month 3	Post-treatment month 6	p
Corneal Staining	2.6±0.11 (1-4)	1.0±0.12 (0-2)	0.5±0.11 (0-2)	0.2±0.08 (0-1)	<0.001
Conjunctival Staining					
Nasal	2.3±0.14 (1-4)	0.8±0.11 (0-2)	0.3±0.08 (0-1)	0.1±0.06 (0-1)	<0.001
Temporal	1.9±0.11 (1-3)	0.6±0.09 (0-1)	0.6±0.09 (0-1)	0.1±0.06 (0.1)	<0.001
Tear Break Up Time (sec)	3.7±0.3 (1-9)	7.3±0.3 (1-11)	9.2±0.2 (7-13)	11.3±0.3 (8-15)	<0.001
Schirmer Score (mm)	6.0±0.4 (1-11)	7.3±0.4 (3-12)	8.8±0.3 (5-12)	9.8±0.3 (8-14)	<0.001
OSDI Score	40.6±1.9 (22.9-38.5)	23.0±1.4 (12.5-45.8)	15.3±1.4 (12.5-45.8)	8.0±0.8 (1.5-18.7)	<0.001
Patient's Subjective Rating Scale	2.2±0.15 (1-4)	1.2±0.122 (0-2)	0.5±0.09 (1-5)	0.5±0.11 (0-2)	<0.001
Daily Use of Artificial Tears	5.5±0.29 (3-9)	2.8±0.19 (1-5)	1.8±0.12 (0-2)	1.0±0.12 (0-2)	<0.001
Global Treatment Response	-	2.5±0.2 (1-5)	1.6±0.1 (1-3)	0.5±0.1 (0-1)	<0.001
CDVA (logmar)	0.03±0.01 (0.00-0.20)	0.02±0.01 (0.00-0.20)	0.00+0.00 (0.00-0.10)	0.00+0.00 (0.00-0.10)	<0.001
IOP (mmHg)	15.5±0.4 (12-20)	15.8±0.4 (12-20)	16.2±0.3 (13-21)	15.7± 0.4 (11-20)	0.654

Researcher's Assesment of the Global Treatment Response

The mean researcher's assessment of the global response to treatment was 2.5±0.2 (1-5) at month 1, 1.6±0.1 (1-3) at month 3 and 0.5±0.1 (0-1) at month 6. Statistically significant improvements in physician's subjective assesment of global response to treatment were observed at all time points ($p<0.001$).

Adverse Events

The most common adverse event reported was ocular burning (6.7%), followed by stinging (3.3%), conjunctival hyperemia (3.3%), foreign body sensation (3.3%), and visual disturbance (3.3%). No other adverse effects were noted.

DISCUSSION

The molecular formula of cyclosporine is $C_{62}H_{111}N_{11}O_{12}$, it is a non-ribosomal peptide containing d-amino acid. The water solubility of cyclosporine is low and its absorption by the cell is variable (13). Cyclosporine can be given to the eye in the form of aqueous drops, but the low dissolution of cyclosporine limits its penetration. Emulsions provide effective topical ophthalmic delivery system with a potential for sustained drug release. In Restasis, 0.05% castor oil is included in the water emulsion. Various other delivery systems are under investigation (14,15).

CsA ophthalmic solution (Restasis) was originally approved by the US Food and Drug Administration for the management of moderate-to severe keratoconjunctivitis sicca (KCS) (severity levels 2-3 in the DEWS guidelines). However, it has been shown that patients with mild dry eye (severity level 1 in the DEWS guidelines) may also benefit from CsA treatment that may reduce the progression of DED severity (16,17). DEWS II cautioned that the management algorithm proposed in their report did not represent rigid stepwise approach (2). In our study, we used topical Cyclosporine whenever the artifical tears or gels were not enough to relieve the symptoms. We did not classify patients according to the type of the dry eye and this might be a limitation of the study.

In Turkey, European Medicine Agency (EMA) rules are applicable for companies to market generic medicines. A generic medicine contains the same active substance as the reference medicine, and it is used at the same dose(s) to treat the same disease. However, a generic medicine's inactive gradients, name, appearance and packaging can be different. Generic medicines are manufactured according to the same quality standards as all other medicines. Since information on the safety and efficacy of the active substance is already available from the reference medicine, companies producing generic medicines usually only need to provide information on the quality of medicine and demonstrate that the generic medicine produces the same levels of the active substance in the human body as the reference medicine. After they have been authorised, the authorites monitor the safety of generic medicines (18). However, many ophthalmologists are concerned about the clinical performance of generic products because of the different pathways that generic and branded ophthalmic medications follow to gain approval (19). Based on this concern, the clinical performance of Depores, a generic CsA 0.05%, has been investigated in this study. To our knowledge, there is no previous clinical study evaluating the efficacy and safety of this generic emulsion.

Several studies and meta-analyses have been published that support the efficacy of cyclosporine in the management of DED (20-23). In multicenter, randomized, double-masked Phase 3 study of Restasis, treatment with CsA 0.05% gave significantly greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). The results of this Depores study are consistent with Phase 3 study of Restasis. Treatment with Depores significantly improved all subjective and objective parameters including corneal staining, Schirmer values, blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment. In this study, we used loteprednol acetate on initiation treatment for a month and this might have played an enhancing role in improvement of signs and symptoms of DED. In a prospective, double-masked, multicenter randomized controlled trial, 0.5% loteprednol therapy two weeks before the initiation of long-term topical 0.05% cyclosporine provided more rapid improvement in Schirmer score, corneal fluorescein staining, lissamine green staining, and symptoms, than topical cyclosporine or artificial tears alone (24). In another prospective study, there was greater reduction in OSDI score, corneal staining, and improvement in TBUT and Schirmer's test values in the group receiving combination of loteprednol 0.5% as compared to the group receiving CsA alone (25).

Topical CsA treatment exhibited a very low rate of of adverse events, and those events seen were mostly mild to moderate. In clinical trials, the most common adverse reaction following the use of Restasis was ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring) (26). In our study, only 2 patients (6.7%) developed burning and 1 patient developed stinging (3.3%), possibly due to initiation treatment with loteprednol as the active/inactive ingredients and pH range of the both formulations (Restasis and Depores) are similar. Previous studies also reported reduced cyclosporine stinging with topical loteprednol (24,25,27). A 36-month extension trial reported lower burning sensation than previously reported in two Phase III 12-month clinical trials suggesting that the side effects are reduced by the improved ocular surface (20). Less stinging in our study might also be related with the level of ocular surface dryness at baseline. There are no systemic side effects in topical use of CsA because very little amount passes into the bloodstream after topical application (14,22).

This study has some limitations such as relatively small number of participants and lack of a control group. However, the study addresses an important issue regarding the clinical performance of a generic CsA ophthalmic emulsion and demonstrated its' efficacy and safety.

CONCLUSION

Depores ophthalmic emulsion twice-a-day with loteprednol etabonate on initiation treatment has well-tolerability and improves subjective and objective measures of dry eye disease.

ACKNOWLEDGEMENTS

Conflicts of Interest: None

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Obstetrics and Gynecology / Kadın Hastalıkları ve Doğum

Effects of Low Back Pain During The First Stage of Labor on Maternal Birth Satisfaction: A Cross Sectional Study

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ABSTRACT

Objectives: Low back pain during labour may occur independently of uterine contractions and may continue without interruption during the labour process. In this study, the characteristics of this pain and its effects on birth satisfaction were evaluated.

Material and Methods: The study was of a cross-sectional study with recurrent measurements and consisted of women in the first stage of labour. Low-risk pregnant women in labour (n=300) were included in the study. Low back pain was repeatedly measured at the different phases of the first stage of the labour. The frequency and severity of low back pain, factors related to low back pain and the effects of pain on maternal satisfaction were evaluated. Descriptive statistics, One-way ANOVA, Cochran's Q test, Logistic regression were used to evaluate the data.

Results: The prevalence of low back pain in latent, active and transitional phases were 38.6%, 60% and 56.6% respectively. Mean pain score statistically, significantly increased from latent phase to active phase. Weight gain in pregnancy, heightened body mass index, occiput posterior presentation and dysmenorrhea were found to be related factors in low back pain. Maternal satisfaction scores were significantly higher in women without low back pain.

Conclusion: Low back pain during labour is often overlooked. This study demonstrated the high frequency of low back pain during labour and its negative effects on birth satisfaction. Especially women with occiput posterior presentation, women with high body mass index and dysmenorrhea are at increased risk.

Keywords: Pain, low back pain, midwives, pregnant, birth, birth satisfaction

Doğumun Birinci Evresindeki Bel Ağrısının Anne Doğum Memnuniyeti Üzerindeki Etkisi

ÖZET

Amaç: Doğum sırasındaki bel ağrısı, uterus kasılmalarından bağımsız olarak ortaya çıkabilir ve doğum sürecinde kesintisiz olarak devam edebilir. Bu çalışmada bu ağrının özellikleri ve doğum memnuniyetine etkileri değerlendirilmiştir.

Gereç ve Yöntem: Çalışma, doğumun ilk evresindeki kadınlardan oluşan, tekrarlayan ölçümlerin yapıldığı kesitsel tipte bir çalışmadır. Doğumdaki düşük riskli gebeler (n=300) çalışmaya dahil edildi. Bel ağrısı, doğumun ilk evresinin farklı evrelerinde tekrar tekrar ölçülmüştür. Bel ağrısının sıklığı ve şiddeti, bel ağrısı ile ilişkili faktörler ve ağrının anne memnuniyeti üzerindeki etkileri değerlendirildi. Verilerin değerlendirilmesinde tanımlayıcı istatistikler, One-way ANOVA, Cochran's Q testi, Lojistik regresyon kullanıldı.

Bulgular: Latent, aktif ve geçiş evrelerinde bel ağrısı prevalansı sırasıyla %38.6, %60 ve %56.6 idi. Ortalama ağrı skoru istatistiksel olarak, latent fazdan aktif faza anlamlı olarak arttı. Gebelikte kilo artışı vücut kitle indeksi, oksiput posterior prezentasyon ve dismenore bel ağrısı ile ilişkili faktörler olarak bulundu. Bel ağrısı olmayan kadınlarda anne doğum memnuniyet puanları anlamlı olarak daha yüksekti.

Sonuç: Doğum sırasındaki bel ağrısı genellikle gözden kaçar. Bu çalışma, doğum sırasında bel ağrısının şiddetini ve doğum memnuniyeti üzerindeki olumsuz etkilerini göstermiştir. Özellikle oksiput posterior prezentasyonu olan kadınlar, vücut kitle indeksi yüksek ve dismenoresi olan kadınlar yüksek risk altındadır.

Anahtar Kelimeler: Ağrı, bel ağrısı, ebe, gebe, doğum, doğum memnuniyeti

One of the most difficult pains experienced by women is pain associated with childbirth. Women have many variations in the perception of the severity of labour pain. Very rarely, some women experience no pain at all while others experience the most severe pain in their life (1,2). There are also variations in the localization of labour pain with Low Back Pain (LBP) being one of these variations. Melzack and Schaffelberg identified three types of pain at different frequencies and characteristics during labour: abdominal contraction pain (96%), intermittent LBP (74%), and continuous LBP (33%). In a recent study, Thezgi and Su (2008) found that 70% of women in labour had LBP (3).

One of the causes of LBP in labour is increased pressure on pain sensitive pelvic structures. Another cause is reflected pain (3,4). Complex nerve distribution of the abdomen and pelvis plays a role in reflected back pain during labour. Spinal cord neurons receive impulses from both the pelvic organs and the surface of the skin (1). As a result of the crossing of the nerve fibers in the dorsal horn of the spinal cord, these two pain pathways are in communication with each other. The sensory cortex cannot distinguish these impulses (5).

Therefore, pain caused by pelvic structures during birth may cause reflected pain in the lumbosacral region.1 In addition, various grades of fetal malpositions, especially occipito-posterior position, have been associated with LBP in labour (6).

Back pain sometimes persists throughout childbirth and continues during periods of contractions. This continuous LBP is seen in 30% of all women during the birthing process (2). In this case, women have no opportunity for rest and relaxation between the contractions (2,7). This leads to fatigue, anxiety, and therefore functional dystocia in women (1,8). In addition, this pain may cause an increase in the frequency of obstetric analgesia applications and associated complications (1).

The term "labour pain" usually refers to the pain caused by uterine contractions and the pain in the back is often overlooked. The presence of low data on the incidences of LBP during birth and related factors have been influential in the planning of this study. There is limited data on the frequency, characteristics, associated factors, and effects on birth satisfaction related to LBP experienced during labour. The purpose of this study was to provide data on these issues.

MATERIALS and METHODS

Design

The study was of correlational and cross-sectional study with recurrent measurements and consisted of women in the first stage of labour. Evaluation of the frequency of LBP during labour, the trend of severity, and the factors that associated LBP constituted the aims of the study. The effect of LBP on birth satisfaction levels was also assessed. In this context, the research questions are as follows;

•What is the incidence of low back pain in the first stage of labor?

•What are the factors that cause low back pain in the first stage of labor?

•What is the effect of pain in the first stage of labor on birth satisfaction?

Study Sample

The study was conducted in a maternity clinic of an education and research hospital in Istanbul between September and November 2016. The population of the study consisted of women who applied to the obstetrics clinic of a training and research hospital in Istanbul between September and November 2016. The population of the study consisted of women who applied to the obstetrics clinic of a training and research hospital in Istanbul between September and November 2016.The sample size of the study was determined based on the findings of a previous study on the subject. According to this study, the prevalence of LBP at labour is 75.3%. When the precision was taken as 5%, the prevalence as 75.3%, and the confidence interval was taken as 95%, the minimum sample size required to detect the prevalence of LBP was calculated as 286.

Participants

Three hundred cases in the early stage of labour (0-4 cm), at gestational weeks 37-42, with low risk, without any complications, and expected vaginal delivery were included in the study. Three cases were excluded from the study due to labour complications, seven cases were excluded as they did not want to take part in the study, so the study was completed with a total of 290 cases (Figure. 1).

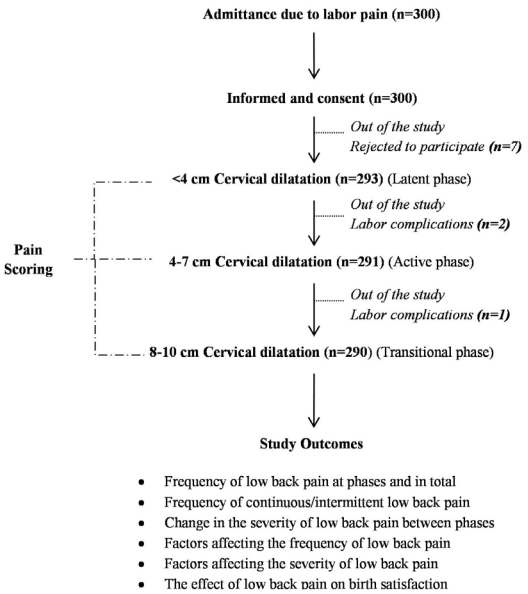

Figure 1: Participant flow and study outcomes

Data Collection

The first stage of labour was examined based on the Early Phase (0-3 cm), Active Phase (4-7 cm) and Transition Phase (8-10 cm). In the early phase (<4cm) the purpose and procedure of study was described to the women, then written and verbal consent was obtained. Socio-demographic information of the women (age, parity, education level, occupation, body weight during hospitalization, gestational weight gain, body mass index, participation in a prenatal education program, dysmenorrhea history, and any presence of pre-pregnancy LBP) was recorded. At the indicated phases of the first stage of labour, women were asked whether they had back pain, and whether the pain was continuous or intermittent.

Measurement

Introductory Information Form: The Introductory Information Form was developed by the researchers in line with the literature. This form consists of 17 questions in total.This form includes questions; Age, Body Weight, Height, Body Mass Index (BMI), Education, Working Status during Pregnancy, Antenatal Follow-up, Prenatal Education, Dysmenorrhea, Low Back Pain during Pregnancy, Low Back Pain in Previous Labor.

Visual Analogue Scale: Pain intensity was assessed by a visual analogue scale. Visual analog scale is used to measure perceived pain. This scale is in a 10 cm line form, with one end refers to "no pain" (0 cm), and the other end refers to (10 cm) "most severe pain". Women were asked to mark a point on the line corresponding to the intensity of pain they feel. The distance from the point that women mark, to the zero point was measured with a ruler and the result was calculated in centimeters or millimeters. It is very easy to use and can be administered in a very short time without any extra burden on women during childbirth. Pain scoring were performed at different stages of the first stage of labor according to cervical dilatation, and immediately before discharge in the postpartum period. A different scale was used for each pain scoring to prevent women from being affected by the previous measurement (9).

The Birth Satisfaction Scale (BSS): The women's birth satisfaction was assessed by the BSS scale before discharge from the hospital. The BSS is a scale of 30 questions developed by Martin and Fleming (10). The total score from the scale ranges from 30-150. This scale was designed to quantitatively measure women's birth experiences. Turkish validity and reliability have been verified by Cetin, Sezer & Doğan (11).

Data Analysis

Percentage, mean and standard deviation were used in the evaluation of the demographic data. Cochran's Q test was used to determine if the percentage of back pain was different at the different phases. A one-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences in pain scores (VAS) over the course of the different phases of the first stage of labour. A binomial logistic regression was performed to ascertain the effects of various factors on the likelihood that participants have back pain during labour. The analyses were performed using Statistical Package for the Social Sciences (SPSS) version 17. A p value of <0.05 was considered statistically significant.

Ethics

The study was conducted in accordance with the Helsinki Declaration Principles, and "Informed consent" was obtained from the cases participating in the study. The ethical committee approval numbered 2016/38 dated 21.09.2016 was obtained from the ethical committee of the hospital where the research was carried out. Additionally, written permission was received from the institutions.

RESULTS

The study was completed with 290 cases (Figure 1). The mean age of the cases was 24.73 ± 5.30. The mean body weight of the cases was 69.82 ± 6.38 kg, and the BMI was 26.66 ± 2.63 kg/m2. Of the cases, 30% were nullipara, 30% were primipara and 40% were multipara.

The majority of the women had a secondary level of education. The regular antenatal follow-up rate was 62.4% and participation in prenatal education classes was 16.5%. The mean weight of newborns was 3211.94 ± 350.82 grams, and the average of head circumference was 35.98 ± 1.20 cm. Of the cases 45.5% had a history of dysmenorrhea. History of back pain before and during pregnancy, and in a previous pregnancy was 52.5%, 34.8% and 33%, respectively. Occiput posterior presentation was seen in 8.9% of cases during labour progression (Table 1).

Low back pain was assessed three times in the first trimester of birth: at the latent phase, active phase, and transition phase. Cochran's Q test was run to determine if the percentage of back pain was different at the different phases. The sample size was adequate to use the χ2-distribution approximation. In the latent phase 38.6% (112 cases) of women had LBP. The percentage of LBP increased to %60 (174 cases) in the active phase and %56.6 (164) in the transition phase. The percentage of LBP was statistically, significantly different at the phases of the first stage of the labour ($\chi^2(2) = 62.131$, $p<0.0001$). Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Adjusted p-values were presented. McNemar's tests were used to assess all pairwise comparisons with the binomial distribution used for small sample sizes. A Bonferroni correction was applied with statistical significance accepted at $p< 0.0167$. Compared to the to the initial (latent phase) percentage of LBP, there was a statistically significant increase in the percentage of LBP in the active phase ($p<0.0001$), and in the transition phase ($\chi^2(1) =26.541$, $p<0.0001$). There was no statistically significant difference in the percentage of LBP between the active phase and the transition phase, p=0.041 (Figure 2).

Table 1. Socio-demographic findings of women (n=290)

	Mean±SD	n	%
Age	24.73±5.30		
Body Weight	69.82±6.38		
Height	161.88±3.76		
BMI	26.66±2.63		
Weight gained during pregnancy	12.13±3.02		
Parity	1.70±1.43		
Nullipara		87	30
Primipara		86	29.7
Multipara		117	40.3
Birth Weight	3211.94±350.82		
Head Circumference	35.98±1.20		
Education			
Primary Education		65	22.4
Secondary Education		157	54.1
Higher Education		68	23.4
Working Status during Pregnancy		89	30.7
Antenatal Follow-up		181	62.4
Prenatal Education		48	16.5
Dysmenorrhea		132	45.5
Low Back Pain during Pregnancy		153	52.8
Low Back Pain outside Pregnancy		101	34.8
Low Back Pain in Previous Labor		67	23.1
OP presentation		26	8.9

SD: Standard Deviation OP: Occiput Posterior Presentation
BMI: Body Mass Index

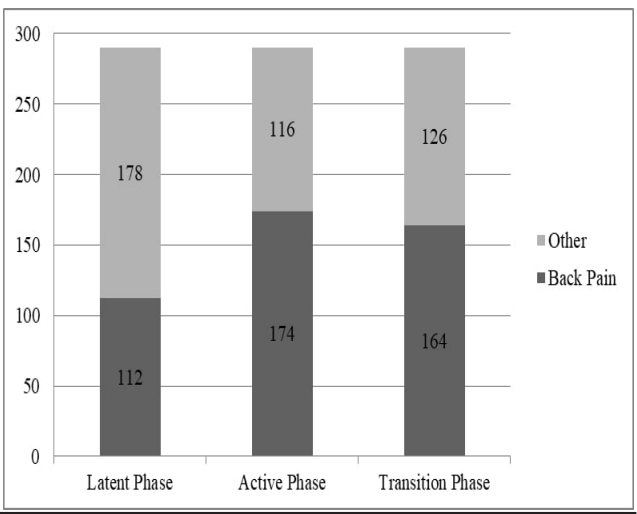

Figure 2: Percentage of LBP in different phases of the first stage of labour (Related Samples Cochran's Q Test

A one-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences in pain scores (VAS) over the course of the different phases of the first stage of labour. There were no outliers and the data was normally distributed, as assessed by the Boxplot and Shapiro-Wilk test (p> 0.05), respectively. The assumption of sphericity was violated, as assessed by Mauchly's test of sphericity, $\chi^2(2) = 5.580$, p=0.045. Therefore, a Greenhouse-Geisser correction was applied (ε=0.889). Progression of labour elicited statistically significant changes in the VAS score over time, F(2,17)=1042.878, p< .0001, partial η^2=0.950, with the mean VAS score increasing from 44.08±5.11 latent phase to 76.08±6.72 at the active phase and to 82.59±8.27 at the transition phase. Post hoc analysis with a Bonferroni adjustment revealed that the mean VAS score was statistically, significantly increased from latent phase to active phase [-31.98 (95% CI, -33.56 to -30.42), p < 0.0001], latent phase to transition phase [-38.50 (95% CI, -40.32 to -36.69), p = 0.001], and active phase to transition phase [(-6.55 (95% CI, -8.48 to -4.53), p<0.0001] (Figure 3).

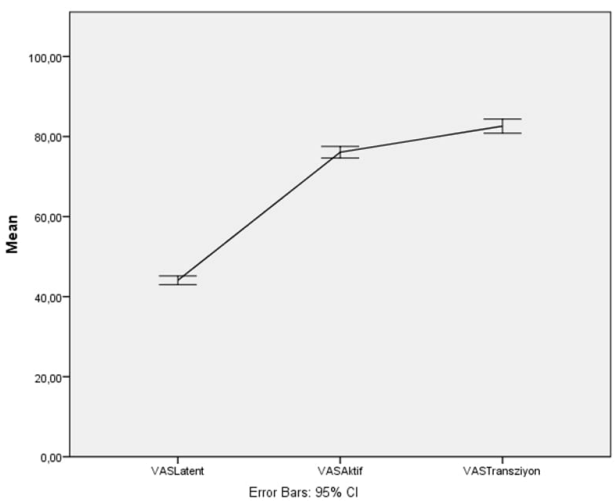

Figure 3: Comparison of mean pain scores between different phases at the first stage of labor

During the latent phase, back pain was continuous in 38.4% of women and intermittent in 61.6%. However, in the majority of women in the active phase and in the transitional phase, the LBP remained largely continuous (67.2% and 76.2%, respectively).

Of the cases, 36.9% (107 women) had LBP in one or two of the three phases. The percentage of women with persistent LBP during all phases of the first stage of labour was 29.7% (86 women). A binomial logistic regression was performed to ascertain the effects of various factors on the likelihood that participants have LBP during labour. The logistic regression model was statistically significant, $\chi^2(12)$ =100.464, p=0.001. The model explained 41.6% (Nagelkerke R2) of the variance in back pain and correctly classified 82.8% of the cases. Sensitivity was 62.8 %, specificity was 91.2 %, the positive predictive value was 75% and the negative predictive value was 85%. Of the thirteen predictor variables, four were statistically significant: weight gain during pregnancy, BMI, history of dysmenorrhea, and occiput posterior presentation (as shown in Table). (Table 2, Figure 4).

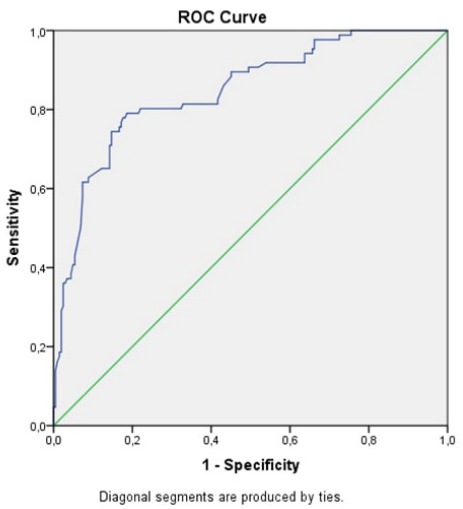

Figure 4: ROC Curve (The area under the ROC curve was 0.846 [95% CI, 0.796 to 0.896])

After the birth, the women were asked about the factors that affected the severity of their LBP. Vaginal examination (46.5%), electronic fetal monitorization (32.6%) and uterine contractions (20.9%) were the most common causes of increased severity of LBP. The most important factor that reduced the severity of LBP was mobilization. Another factor that reduced the pain was the change in position.

Table 2. Logistic regression predicting likelihood of Low Back Pain during first stage of labor

Predictor variable	Exp (B)	95% C.I.for EXP (B)	P value
Age	0.987	0.888 – 1.098	0.814
Parity	4.208	1.455 – 12.170	0.04
0 (reference)			
≥1			
BMI	2.755	1.266 – 5.994	0.011
<28 kg/m2 (reference)			
≥28 kg/m2			
Weight put on during pregnancy	2.436	1.048 – 5.659	0.038
<12 kg (reference)			
≥12 kg			
Pre-pregnancy low back pain	0.391	0.676 – 0.277	0.391
No (reference)			
Yes			
LBP during pregnancy	1.375	0.629 – 3.002	0.425
No (reference)			
Yes			
History of dysmenorrhea	5.065	2.270 – 11.302	<0.001
No (reference)			
Yes			
Birth weight	0.979	0.476 – 2.015	0.954
<3200 gr (reference)			
≥3200 gr			
Working during the pregnancy	1.791	0.729 – 4.398	0.204
No (reference)			
Yes			
Antenatal follow-up	2.003	0.825 – 4.862	0.125
No (reference)			
Yes			
Prenatal training	1.326	0.558 – 3.152	0.523
No (reference)			
Yes			
OP presentation	6.402	1.999 – 20.503	0.002
No (reference)			
Yes			

OP: Occiput Posterior BMI: Body Mass Index

A one-way Welch ANOVA was conducted to determine if the BSS scores were different between the groups. Participants were classified into 3 groups: women with no LBP (n=97, GA), women with LBP in one or two phases (n=107, GB) and women with LBP in all phases (GC, n=86). There were no outliers and the data was normally distributed for each group, as assessed by the Box-plot and Shapiro-Wilk test ($p < .05$). Homogeneity of variances was assessed by Levene's Test of Homogeneity of Variance ($p = 0.001$). The BBS scores were significantly different between the LBP groups, Welch's $F(2, 189.595) = 77.008$, $p<0.0001$. The BSS scores decreased from the GA (107.78±11.13) to the GB (93.41±10.03), and GC (90.63±7.96). The Games-Howell post hoc analysis revealed that the decrease from GA to GB was statistically significant [14.37, 95% CI (11.11 to 17.63), $p <0.001$], as well as decrease from GA to GC [17.14, (95% CI 13.69 to 20.58), $p< 0.001$)]. There was no statistically significant difference in BSS scores between GB and GC [2.77, (95% CI -0.59 to 6.13), $p=0.130$)]. The BSS score was statistically, significantly higher in the GA (107.78±11.13) compared to women with LBP in at least one of the three phases (GB+GC, mean of 92.02), a mean difference of 15.75 (95% CI, 12.794 to 18.723), $p< 0.001$. (Figure 5).

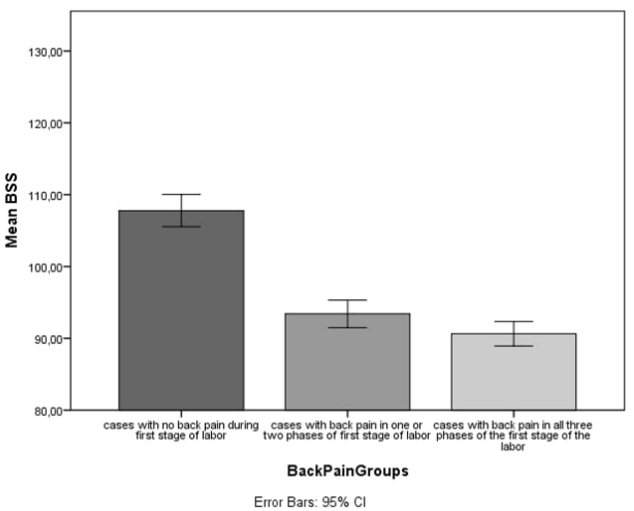

Figure 5: Comparison of the mean Birth Satisfaction scores (BSS) between the different LBP groups according to frequency

DISCUSSION

Giving birth is a physiological and psychological experience for women. Labour pain is considered one of the severest types of pain and is affected by physiological and psychological factors (2,6,12). While some women never feel labour pain for others it is the severest pain they have experienced in their lives (1,2). Labour pain comes from different regions in the body and at different phases in the birthing process. In the first phase, it is seen during contractions and it is visceral or cramping. It begins in the uterus and cervix and is caused by the stretching of uterine structures and cervical dilatation. It is carried to the medulla spinalis by spinal nerves at the T10-L1 level. It can be felt in the abdomen, lumbosacral, iliac crest, gluteal region and thighs (13). Among these, low back pain can be seen as pain resulting from pain-sensitive structures being pressed or as a reflective pain (3,13).

One of the first studies to draw attention to LBP experienced by women during labour was done by Bonica.4 A few years later, Melzack and Schaffelberg performed one of the most important research studies on the subject (5).

In the following years, studies have been carried out investigating various methods for reducing LBP during labour. One of the most popular of these was the application of a sterile water injection. Studies examining the effects of sterile water injection on LBP seen during labour have shown the importance of this pain. However, our knowledge about the frequency and characteristics of this pain is limited. This study shows that women also have high incidences of LBP as well as abdominal pain during labour. While 36.9% of the women had LBP in one or two of the three phases, in 29.7%, LBP was persistent throughout the first stage of labour. In Melzack and Schaffelberg's study (3), 33% of the women in the first stage of labour had LBP. The same rate was given as 75.3% in the study of Tzeng and Su (14). In this study the frequency of LBP at different phases of the first stage of labour was also assessed. Frequency was lowest in the latent phase (38.6%). In the active phase this frequency increased approximately 1.5-fold (60%), and in the transitional phase, no significant difference was observed compared to the active phase (56.6%).

In some studies that examine the effect of sterile water injection on low back pain, the severity of low back pain was measured in the study at different intervals from the placebo groups. However, no data was found regarding the differences between the phases. Lee, Kildea & Stapleton, stated that the LBP in labour was severe enough to keep all the physical senses away from the mind (5). Women have described the the pain as their bones being crushed or fractured. Many of the women have stated that the pain starts from the early stages of labour and requires professional help and analgesia. Tzeng and Su reported the severity of the low back pain evaluated by VAS was between 36.66-76.20 during the first phase (14). It was stated that as the first stage progressed, the severity of the low back pain increased. In our study, wherein the pain was scored at similar time intervals, the differences between the intensity of pain between the phases of the first stage were evaluated using A one-way repeated measures ANOVA. It was found that pain scores were significantly different between the first stage phases and increased with the progression of labour. Planned contrasts showed that the pain score statistically, significantly increased from the latent phase to the transition phase, a mean difference of -38.50 [95% CI, -40.59 to -36.42), ($p = 0.0001$]. In addition, there was a statistically significant increase in VAS score from the latent phase (44.08±5.11) to the average of the active (76.08±6.72) and transition phase (82.59±8.27), a mean difference of -35.253 (95% CI, -36.83 to -33.67) mg/L, $p < 0.0001$, $\eta 2 = 0.95$.

Another feature of low back pain which is as important as its frequency and severity is whether it is continuous or intermittent. Sometimes it can be persistent even between contractions.7 In such cases, it has been reported that it is more difficult to cope with contractions, as the woman is deprived of the normal painless intervals required for rest (15).

This frequency of continuous low back pain was reported as 33% and 45.71% in the studies of Melzack and Schaffelberg, (3) and Tzeng and Su (14) respectively. In this study, the frequency of continuous back pain was found to be 38.4% in the latent phase. It was 67.2% in the active phase and 76.2% in the transitional phase. This result shows that there is an increase in the continuity of the first stage progression as well as the frequency and severity of low back pain. Continuous low back pain is most probably the result of the fetal pressure on the pain-sensitive structures on the pelvis (3).

Low back pain in labour is frequently accompanied by occipito-posterior position (16). It was reported that introduction and progression of the fetus with a larger diameter in the maternal pelvis and the decrease in the fetal head and maternal cervical contact may lead to ineffective contractions, dystocia, slow progression in the first and second phase and increased pain (17,18). Previous history of back pain, dysmenorrhea, history of low back pain in pregnancy, and excessive weight are considered to be associated with low back pain in labour (2,14,19).

Excessive weight can have an effect on the increase in the pain due to the pressure and load on the pelvic organs. Melzack and Bélanger (19) reported that there was a significant correlation between dysmenorrhea and birth pain, and this result showed that both cases had a common mechanism. They found that prenatal episodic low back pain was not correlated with any of the birth pains but acute low back pain during pregnancy was correlated with low back pain observed in labour. According to the logistic regression analysis conducted in this study, weight gain, BMI, history of dysmenorrhea and OP presentation during pregnancy were determined as the factors that increased the frequency of low back pain. Women who have gained 12 or more kilos in pregnancy have a 2.436-fold odds for LBP. Women with BMI ≥28 kg/m2 have 2.755, women with a history of dysmenorrhea have 5.065, women with occiput-posterior presentation have 6.402-fold odds for LBP during their first stage of labour. Vaginal examination, EFM, external factors that increase back pain, mobilization and posture changes were found to be external factors.

The birth satisfaction of women has long-term and short-term effects. Low satisfaction in labour is associated with postpartum psychiatric disorders, poor communication with the neonate, postpartum fear and future C-section birth (20). Birth satisfaction can be thought to be influenced by other factors such as socio-cultural factors, antenatal education, previous experiences, and the care given in labour. However, pain and pain management is the most common among these factors (20). This study showed the negative effects of low back pain, which may be a component of labour pain, on birth satisfaction of women. Birth satisfaction scores are significantly higher in women without low back pain than in women with low back pain in at least one phase of the first phase of labour.

Limitations

This study was limited to the pregnant women who agreed to participate in the study. Therefore, the findings are limited only to the sample of this study and cannot be generalized; that is, they can only be applied to the study sample.

CONCLUSION

It was shown in the study that low back pain in the first stage of birth was a frequent and severe pain modality in labour, severity of labour pain gradually increased as labour progressed and that it might have negative effects on birth satisfaction scores. Therefore, it is important to investigate the low back pain in women who are admitted due to labour pain, evaluate the problem in terms of risk factors (BMI, dysmenorrhea and OP), and to follow up during labour progression.

Management of individual low back pain should be planned in order to prevent low birth satisfaction and its negative effects, reduce the severity of pain and provide a more comfortable birth experience for women. It is also important to avoid unnecessary examinations and EFM, and encourage women to be mobile and make posture changes. When needed, pharmacological analgesic methods or non-pharmacological (biofeedback, motion, hypnosis, acupuncture, acupressure, music sofrology, haptonomy, vocalization; focusing, distraction, daydreaming; intradermal sterile water injection, TENS, massage, aramotherapy, hot application, hydrotherapy; lamaze, dick read) can be applied (21).

In this context; midwives and nurses working in maternity wards play a key role in the management of pain. Midwives and nurses should meet the physical and psychosocial care needs of every woman during pregnancy and help her cope with the labour pain. For this purpose, midwives and nurses should know pharmacological and non-pharmacological methods of coping with pain and apply them effectively.

It was shown in the study that low back pain in the first stage of birth was a frequent and severe pain modality in labour, severity of labour pain gradually increased as labour progressed and that it might have negative effects on birth satisfaction scores. Therefore, it is important to investigate the low back pain in women who are admitted due to labour pain, evaluate the problem in terms of risk factors (BMI, dysmenorrhea and OP), and to follow up during labour progression.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Obstetrics and Gynecology / Kadın Hastalıkları ve Doğum

Relationship of Self-Compassion with Anxiety and Depressive Symptoms in Infertile Women

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ABSTRACT

Purpose: Infertile women have a higher rate of psychiatric symptoms compared to fertile women while depression and anxiety are among the most common psychiatric disorders in this group. Self-compassion might be a variable in predicting depression, anxiety and stress. The study aimed to evaluate self-compassion in infertile women and to examine its relationship with depression and anxiety levels.

Methods: This cross-sectional study included a total number of 122 participants. The study group (n=50) consisted of women who applied to the gynaecology and obstetrics clinic for infertility treatment and were recruited consecutively. The control group (n=72) was recruited from hospital staff and their relatives, of the similar age and gender as the study group. The participants filled Self-Compassion Scale (SCS) and Hospital Anxiety and Depression Scale (HADS) in addition to sociodemographic data form.

Results: SCS scores were significantly lower, and HADS scores (both depression and anxiety) were significantly higher in the study group, compared to the control group. There was a negative correlation between SCS and HADS scores ($p < 0.001$), indicating that lower self-compassion levels are associated with increased depression and anxiety. Duration of infertility treatment was not correlated with SCS and HADS scores ($p > 0.05$).

Conclusion: Infertile women have higher levels of depression and anxiety while self-compassion is an influential factor in maintaining psychological well-being and preventing anxiety and depressive symptoms in this group. Self-compassion based or other interventions targeting psychological well-being of infertile women would be beneficial.

Keywords: Anxiety; Self-Compassion; Depression; Female; Infertility; Psychological Factors

İnfertil Kadınlarda Özşefkat ile Anksiyete ve Depresif Belirtiler Arasındaki İlişki

ÖZET

Amaç: İnfertil kadınlarda fertil kadınlara göre psikiyatrik belirti gözlenme oranı daha fazladır ve depresyon ile anksiyete bu gruptaki en yaygın psikiyatrik rahatsızlıklardandır. Özşefkat; depresyon, anksiyete ve stresi öngörmekte değerli bir değişken olabilmektedir. Çalışmamız infertil kadınlarda özşefkati değerlendirmeyi ve depresyon ve anksiyete düzeyleri ile ilişkisini incelemeyi amaçlamaktadır.

Yöntem: Bu kesitsel araştırmanın örneklemi 122 hastadan oluşmaktadır. İnfertilite tedavisi için kadın hastalıkları ve doğum kliniğine başvuran kadınlar ardışık olarak çalışma grubuna (N=50) dahil edilmiştir. Kontrol grubu (N=72) ise hastane çalışanları ve akrabalarından, benzer yaş ve cinsiyet gözetilerek seçilmiştir. Katılımcılar sosyodemografik veri formuna ek olarak Öz-Anlayış Ölçeği (SCS) ve Hastane Anksiyete ve Depresyon Ölçeği (HADS) formlarını doldurmuşlardır.

Bulgular: Kontrol grubu ile karşılaştırıldığında, çalışma grubunda SCS skorları anlamlı olarak düşük ve HADS skoru (depresyon ve anksiyete) anlamlı olarak yüksek bulunmuştur. SCS ve HADS skorları arasında negatif korelasyon tespit edilmiştir ($p < 0.001$). Bu ilişki, düşük özşefkatın yüksek depresyon ve anksiyete ile bağlantılı olduğunu göstermektedir. İnfertilite tedavisinin süresi SCS ve HADS skorları ile bağlantısız bulunmuştur ($p > 0.05$).

Sonuç: İnfertil kadınlarda depresyon ve anksiyete düzeyleri daha yüksek saptanmakta olup, özşefkat bu grupta psikolojik sağlığın korunması ile anksiyete ve depresif belirtilerin önlenmesinde etkili bir faktördür. İnfertil kadınların psikolojik iyi oluşlarını hedefleyen özşefkat temelli ya da diğer girişimler yararlı olacaktır.

Anahtar Sözcükler: Anksiyete; Özşefkat; Depresyon; Kadın; İnfertilite; Psikolojik faktörler

Infertility is defined as failure of conception after one year of unprotected intercourse in the fertile phase of the menstrual cycles and it is estimated that impaired fertility affects 10–15% of couples (1). Eventually, advances in medicine have opened up the possibility of diagnosis and treatment in many cases of infertility, as well as the use of assisted reproductive techniques enabling conception in many couples (2).

Infertility, which is generally considered as a stressful period for the couple, is particularly accepted as a devastating experience for women (3, 4). The prevalence of psychiatric disorders was found to be higher in infertile women compared to fertile women (5, 6). In women who applied to assisted reproductive treatment, the rate of psychiatric disorders was determined as high as 40.2% (7). Depressive symptoms and anxiety are among the predominant psychiatric symptoms in infertile women (2, 7, 8, 9). Studies revealed that the prevalence of major depression and anxiety disorder in this group was as high as 17.0%, and 28.6%, respectively (7, 9).

The term self-compassion, developed by Neff (10), signifies being open to one's own suffering along with a kind and caring approach toward oneself. It involves an understanding, nonjudgmental attitude toward one's pain, inadequacies and failures, and recognizing it as a part of the common human experience. Self-compassion stands out as a positive factor in terms of coping, life satisfaction and psychological well-being. It has been suggested that people with high self-compassion levels have lower levels of depression and anxiety when faced with a stressor (11). In a limited number of studies in the literature focusing on self-compassion in infertile women, self-compassion has been reported as a protective factor in terms of fertility-related distress (12). It is found to be associated with subjective well-being, hope and decreased social stigma in infertile women (4, 13). Self-compassion comes to the fore in predicting depression, anxiety, and stress among women with infertility (14), certainly creating the need for further research in this area.

MATERIALS AND METHODS

The study was conducted in Acıbadem University Atakent Hospital in a 2-month period.

Ethics committee approval (approval number 2021-19/01) was obtained from the same institution for the study. The study group consisted of women who applied to Gynecology and Obstetrics outpatient clinic with the complaint of infertility for treatment purposes. Fifty consecutive patients who agreed to participate in the study and filled out the study forms and scales completely were included in the study. Exclusion criteria for the study group were illiteracy and the presence of severe psychiatric disorders such as psychotic disorders or mental retardation. Simultaneously, it was aimed to reach a similar number of participants for the control group, consisting of hospital staff and their relatives. The people who participated in the study via googleforms in the same time period were included in the control group. According to the answers given to the questions in the study form, people who have received or are still receiving infertility treatment were subsequently excluded from the control group.

The questions were given to the study group in print. For the control group, the questions were prepared via googleforms and sent by sharing the link via text message. The printed forms begin with the Informed Consent Form giving information about the study. The survey in googleforms also starts with the Informed Consent Form and the question of confirming participation in the study, and it is not possible for the participants who do not give consent to proceed. After the Informed Consent Form, Sociodemographic Form, Self-Compassion Scale, Hospital Anxiety and Depression Scale were used during data collection.

Sociodemographic Form

It is a short form consisting of questions about the sociodemographic characteristics as well as the past infertility treatment. It was developed by the researchers in line with the purpose of the study.

Self-Compassion Scale (SCS)

The scale was developed by Neff (10) to measure individuals' self-compassion level. The Turkish validity and reliability study was conducted by Deniz et al. (15). The Likert-type self-rating scale, which originally consisted of 26 items and each item was scored between 1 and 5, was adapted into Turkish as 24 items. Higher scores of the scale indicate higher self-compassion levels.

Hospital Anxiety and Depression Scale (HADS)

The scale aims to measure the anxiety and depression levels of the participants. The Turkish validity and reliability study of the scale was performed by Aydemir et al. (16). The self-rating scale consists of a total of 14 items and 2 subscales, 7 of the items question symptoms of anxiety

and 7 of them question symptoms of depression. Higher scores indicate higher levels of anxiety and depression.

Data Analysis

All the data obtained in the study was analyzed using the SPSS 21.0 package program (SPSS Inc., Chicago IL, USA). Skewness and kurtosis indices, histogram graph, QQ plot graph, and Kolmogorov-Smirnov normality test were used to determine whether the variables showed a normal distribution. Descriptive statistics were used to determine the participants' characteristics. An independent t-test was used to examine the self-compassion, HADS anxiety, and HADS depression scores between groups. The correlations between the normally distributed scale scores were analyzed by Pearson analysis. Spearman analysis was applied to correlate the scales with the duration of infertility treatment, which is non-normally distributed. In addition, a Multiple Linear Regression Analysis was applied to show the mediating effect of total self-compassion score. A $p \leq 0.05$ was considered statistically significant.

In the post hoc power analysis, the effect size was found to be 0.411 and the power analysis of the study was 0.613 in terms of the results of SCS scores between two groups.

RESULTS

The study group consisted of 50 women who applied to the gynaecology and obstetrics clinic for infertility treatment and were recruited consecutively. In the control group, 10 of the 87 participants were excluded from the study because they had received infertility treatment in the past, and 5 participants were excluded because they filled the forms incompletely. The mean age of the study group was 31.50 (n=50, sd. 5.104), while the mean age of the control group was 31.86 (n=72, sd. 7.681). There was no significant difference between the groups in terms of age. Considering the education levels, 18 (36%) of the study group were primary school graduates, 23 (46%) were high school graduates, and 9 (18%) were university graduates. In the control group, 11 were high school (15.3%) and 61 (84.7) were university graduates. There were 28 (38.9%) participants in the control group who had children with the mean number of children 0.54 (sd. 0.768). The mean duration of infertility treatment in the study group was 5.48 months (sd. 5.023). Six (12%) participants in the study group had a history of unsuccessful infertility treatment in the past.

The independent samples t-test was used to compare the infertility treatment group with the control group in terms of SCS and HADS scores. Self-compassion scores were significantly lower and depression and anxiety scores were significantly higher in the study group, compared to control group. The details of the comparison are given in Table 1.

Table 1. Comparison of Self-Compassion and Hospital Anxiety and Depression Scale Scores Between Groups

	Study Group (n = 50)	Control Group (n = 72)	t	df	*p*
Self-Compassion Scale	71.12 (sd.17.779)	78.708 (sd.19.273)	2.207	120	**.029**
HADS Anxiety	9.36 (sd. 5.363)	7.319 (sd. 4.424)	2.295	120	**.023**
HADS Depression	6.80 (sd. 5.387)	5.041 (sd. 3.694)	2.14	120	**.034**

Student t-test, sd=standart deviation, df: degrees of freedom, t: t value.

The correlations between the scales were analyzed by Pearson correlation analysis, it was found that there is a negative correlation between SCS and HADS depression and anxiety scores (Pearson correlation coefficient 0.727 and 0.656, respectively, $p < 0.001$). In addition, HADS depression and anxiety scores show a positive correlation with each other (Pearson correlation coefficient 0.848, $p < 0.001$). Spearman correlation analysis was applied to examine the correlation between the duration of infertility treatment (in months) and the scale scores and this variable did not show a significant correlation with self-compassion, anxiety, and depression scores ($p > 0.05$).

We applied linear regression analysis to test our hypothesis that self-compassion has a mediating effect on depression and anxiety in women undergoing infertility treatment. Because HADS anxiety and depression scores showed a high correlation with each other, they were combined and included in the analysis as a single score. The result of the linear regression analysis is shown in Table 2. As a result of multiple linear regression analysis, the decrease in self-compassion total score and infertility and/or receiving infertility treatment explained 52.3% of the increase in HADS scores. It is seen that a significant part of this effect comes from the self-compassion score. As shown in Table 1, it was found that infertility/receiving infertility treatment led to a significant increase in HADS scores. As a result of our multiple linear regression analysis, it is seen that this effect occurs as a result of the mediator effect of self-compassion scores.

Table 2. The effect of self-compassion total score and infertility treatment on HADS scores: Multiple Regression Analysis

	B	Std. error	Beta	t	p-value	95.0% CI for B
Constant	39.018	2.506		15.572	<.001	34.056 to 43.979
Infertility Treatment	1.229	1.170	0.67	1.051	.295	-1.087 to 3.545
Self-compassion Total Score	-.339	.03	-.716	-11.127	<.001	-.399 to -.278

R: .729, Adjusted R^2: .523.
B: Unstandardized Regression Coefficient, CI: Confidence Interval, HADS: Hospital Anxiety and Depression Scale

DISCUSSION

Psychological factors associated with infertility have been the subject of many studies, still whether stress and infertility are related as cause or consequence is controversial (3). Some authors have suggested that psychological factors may play a role in the emergence of infertility. It has been suggested that high anxiety levels have a negative effect on conception rates (17, 18). However, psychological problems arised as a consequence of infertility have come to the fore more.

Although infertility is considered a stressful period for spouses, it is underlined that it is challenging especially for women (3, 4). One of the the factors that affect the higher level of stress is the limitation brought by the reproductive age of women (19). In addition, the social stigmatization of women by being held responsible for infertility, as well as the fact that having a child plays a crucial role in women's identity and status in social life in some societies, contributes the stress level of women (2, 4). The emergence marital dissatisfaction in infertility and considering having children as a source of maintaning the foundation of the family may also increase the pressure on women (4).

While assisted reproductive techniques such as IVF help infertile couples to obtain conception, the treatment process is especially challenging for women due to reasons such as hormonal changes and medical interventions faced by women during this course. Uncertainity is a significant stressor as well as the fear of treatment failure and inability to conceive (19, 20, 21).

Psychological distress is common in infertile women, even many women report the evaluation and treatment of infertility as the most upsetting experience of their lives (2). Psychiatric symptoms and disorders were reported more in infertile women compared to fertile women or general population (5, 6, 7). Noorbala et al. (5) found that 44% of infertile women had a psychiatric disorder, this rate is significantly higher compared to fertile women (28.7%). Anxiety and depressive symptoms are among the most investigated symptoms and were found at higher rates in infertile women in many studies (7, 21). It has been underlined that individuals receiving assisted reproductive therapy are particularly at risk for psychiatric disorders. The rate of psychiatric disorders in women applying for assisted reproductive treatment has been reported as high as 40.2% (7, 9). Anxiety and depressive disorders are among the most prevalent disorders in this group (9). Major depressive disorder was reported in 39% of women receiving infertility treatment (22). Among women preparing for assisted reproduction treatment, 26.8% found to have depressive disorders and 28.6%, anxiety disorders (7). In an another study, women who applied to infertility clinics, were exibiting significant symptoms of depression (56%) and anxiety (76%) (23).

In our study, depression and anxiety levels determined by HADS were found to be significantly higher in infertile women compared to the control group. This finding is consistent with similar studies using rating scales and self-administered questionnaires. In fact, the HADS scale averages in our study (depression score 6.8 ± 5.3, anxiety score 9.3 ± 5.3) were found to be higher compared to similar studies. In a study using HADS in infertile women, mean depression score was 4.6 ± 3.1, mean anxiety score was 6.7 ± 3.5 (7). In another study, the HADS depression score was 4.6 ± 2.9 and the anxiety score was 6.9 ± 3.1 (21).

The duration of infertility has been reported as a factor that increases the stress level in infertile women (19). There are studies reporting that the length of the treatment period also increases emotional stress (24). On the contrary, there are studies reporting that previous assisted reproductive treatments do not affect depression and anxiety levels (7). In our study, the duration of infertility treatment and unsuccessful treatment attempts in the

past were not found to be associated with anxiety and depressive symptoms or self compassion levels.

Compassion may be described as being aware and sensitive to others' suffering with the desire to alleviate it and self-compassion may be explained simply as compassion directed inward. The three main elements of self-compassion are self-kindness (versus self-judgement), a sense of common humanity (versus self-isolation), and mindfulness (versus overidentification) (25). It is suggested that self-compassion provides emotional resilience when faced with difficult life experiences such as grief, sadness, burnout and failure. Increased self-compassion was found to be associated with decrease in shame and guilt and improvement in interpersonal relationships (15, 25). Self-compassion stands out as a positive factor in terms of coping, life satisfaction and psychological well-being. It has been suggested that people with high self-compassion levels have lower levels of depression and anxiety when faced with a stresful life event (11).

It has been reported that infertile individuals, especially women, tend to exibit more self-judgment and less self-compassion (26). The association between self-compassion and infertility-related distress is consistent in the literature (4, 13, 26). Further, lower self-compassion levels were found to be associated with depression and anxiety in infertile women (14). In our study, self-compassion levels were found to be significantly lower in the study group compared to the control group. In addition, lower self-compassion levels were found to be related with anxiety and depressive symptoms in this group. Such findings reveal that self-compassion is an important variable in associated with psychological symptoms in infertile women.

Women may hide their distress from health providers because they are self-conscious, afraid of being criticized, or stigmatized. Also they may not perceive the need for counseling (2). Many clinicians conducting infertility treatment rarely require consultation with a counselor before or during fertility treatment, and special issues such as multiple miscarriages, which may require psychological support are often not adequately addressed (27). These can prevent infertile women from getting the psychosocial support they need.

It has been reported in the literature that psychological interventions can reduce distress associated with infertility (2). A comprehensive review concluded that psychotherapy (either group psychotherapy or individual/couple psychotherapy) caused a decrease in anxiety and depressive symptoms in infertile individuals (28). A study investigating the effectiveness of counseling during the IVF process, revealed that the couples receiving counseling had significantly lower anxiety and depression scores, higher life satisfaction and higher pregnancy rates compared to the controls (29). Mind-body programs targeting infertile couples including relaxation techniques, stress management, coping-skills training and group support have also been found beneficial (30). Self-compassion could be an important variable for the management of infertility-related psychological symptoms. Hence, improvement in psychological well-being was observed in infertile women who received self-compassion training (4).

To the best of our knowledge, our study is the first in Turkey to investigate self-compassion levels in infertile women and to evaluate self-compassion as a mediator in terms of anxiety and depressive symptoms in this group. Our study has some limitations such as: Since it is carried out in a single center, it is not sufficient to generalize the results. The use of self-rating scales causes participants to report their symptoms subjectively. The absence of a structured psychiatric interview does not allow for a definitive diagnosis.

In infertility, the role of the physician is crucial, not only carrying out the diagnosis and treatment process in the best way, but also providing and supporting the mental well-being of the infertile woman. In this respect, it is important to screen this group for psychological symptoms, especially anxiety and depression. Patients who experience anxiety and/or depressive symptoms should be referred to a mental health professional. Interventions that will increase the psychological well-being of infertile women are fundamental. Self-compassion stands out as an effective factor in maintaining psychological well-being and preventing anxiety and depressive symptoms in infertile women. Accordingly, practices to increase self-compassion will be beneficial, as well as further research in this area.

DECLARATIONS

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Data Availability: Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Orthopedics / Ortopedi

Could Sea Wave-Like Sign Be Used in the Diagnosis of Adult Simple Elbow Dislocations?

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ABSTRACT

Purpose: The elbow is the second most dislocated major joint in adults. This study aimed to evaluate the reliability of the use of 'sea wave-like sign' in adult simple elbow dislocation.

Methods: The study included 12 randomly selected adults with simple elbow dislocation cases. All patients were evaluated with pre-reduction and post-reduction radiographs. The definitive diagnosis of reduction was made with post-reduction CT. Evaluations were performed by five orthopedic residents (Group I), five orthopedic specialists with less than 10 years of professional experience (Group II), and five orthopedic specialists with more than 10 years of professional experience (Group III). They were requested to fill out a questionnaire including the reduction and 'sea wave-like sign'.

Results: The specificity of the sea wave-like sign on radiography was 96.6% and the positive predictive value of this evaluation was 99.1%. There were statistically significant differences between the groups in terms of evaluation of the reduction of the elbow joint. The correct response rates in young specialists were significantly lower than the other two groups ($p<0.05$). There were no statistically significant differences between the groups in terms of evaluation of the presence of 'sea wave-like sign' ($p=0.266$).

Conclusion: Sea wave-like sign could be used for adult simple elbow dislocation. The 'sea wave-like sign' could reduce the need for CT in a simple elbow dislocation.

Keywords: CT, radiography, sea-wave like sign, simple elbow dislocation

Erişkin basit dirsek çıkıklarının tanısında deniz dalgası benzeri işaret kullanılabilir mi?

ÖZET

Amaç: Dirsek, yetişkinlerde en çok çıkık olan ikinci ana eklemdir. Bu çalışmanın amacı, erişkin basit dirsek çıkığında 'deniz dalgası benzeri işaret' kullanımının güvenilirliğininin değerlendirilmesidir.

Yöntem: Çalışmaya basit dirsek çıkığı olan rastgele seçilmiş 12 yetişkin vaka dahil edildi. Tüm hastaların redüksiyon öncesi ve redüksiyon sonrası radyografileri değerlendirildi. Dirsek redüksiyonunun değerlendirilmesinde kesin tanı yöntemi olarak BT kullanıldı. Değerlendirmeler beş ortopedi asistanı (Grup I), 10 yıldan az mesleki deneyime sahip beş ortopedi uzmanı (Grup II) ve 10 yıldan fazla mesleki deneyime sahip beş ortopedi uzmanı (Grup III) tarafından yapılmıştır. Çalışmadaki 15 hekimden redüksiyonu ve 'deniz dalgası benzeri işareti' değerlendirmeleri istendi.

Bulgular: Radyografide deniz dalgası benzeri işaretin özgüllüğü %96,6 ve bu değerlendirmenin pozitif prediktif değeri %99,1 olarak tespit edildi. Dirsek eklemindeki redüksiyonun değerlendirilmesi açısından gruplar arasında istatistiksel olarak anlamlı farklılıklar vardı. Genç uzmanlarda doğru yanıt oranları diğer iki gruba göre anlamlı derecede düşük olarak gözlemlendi ($p<0.05$). Deniz dalgası benzeri işaret varlığının değerlendirilmesi açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ($p=0,266$).

Sonuç: Yetişkin basit dirsek çıkığı için deniz dalgası benzeri işaret kullanılabilir. Deniz dalgası benzeri işaret, basit bir dirsek çıkığında BT ihtiyacını azaltabilir.

Anahtar Kelimeler: BT, radyografi, deniz dalgası benzeri işaret, basit dirsek çıkığı

The elbow is the second most dislocated major joint in adults (4,8,16). They could be simple dislocations that involve only ligamentous and soft tissue injuries or complex dislocations that include bony injuries (4).

Closed reduction is the first step in the management of elbow dislocations. The instability could be manifest with elbow dislocation in some cases. At that time, it is not easy to decide the reduction of the elbow joint with direct radiography. Some criteria were defined previously, but they were often insufficient (10). No consensus has been yet reached on a gold standard method. Therefore, computed tomography (CT) is often used to decide the reduction of the elbow joint.

Previously a new diagnostic radiological criteria, 'sea wave-like sign', was defined to facilitate the diagnosis of incarcerated medial epicondyle fractures in children (12). 'Sea wave-like sign' also could be used for adult simple elbow dislocations (SED) in adults. Hence, the aim of this study was to evaluate the reliability of the use of 'sea wave-like sign' in adult SED.

MATERIALS AND METHODS

A retrospective review was made of a hospital electronic database to obtain details of patients with adult SED who were treated between January 2015 and April 2018 at Ankara Numune Training and Research Hospital. The study was approved by the Institutional Review Board (E-18-2446). Twelve randomly selected cases selected by an evaluator, suitable for radiological and CT examinations, were included in the study.

Adult SED, patients whose pre-reduction and post-reduction radiographs could be reached, and patients whose post-reduction computed tomography were included in the present study. Patients under 18 years, patients with previous elbow fracture on the same side, insufficient data, and periprosthetic fractures were excluded.

Previously a new diagnostic radiological criteria, 'sea wave-like sign', was defined to facilitate the diagnosis of incarcerated medial epicondyle fractures in children (12). A parallel double line was seen as a 'sea wave-like sign' on the anterior-posterior elbow radiographs of non-fractured or reduced pediatric patients. The parallelism was seen as disrupted in incarcerated medial epicondyle fractures. The incarcerated fragment distracted in the joint space in the medial compartment of the elbow between the trochlea of the humerus and coracoid of the ulna leads to disruption of this parallel double line. The 'sea wave-like sign' could be seen in adult SED (Figure 1, Figure 2).

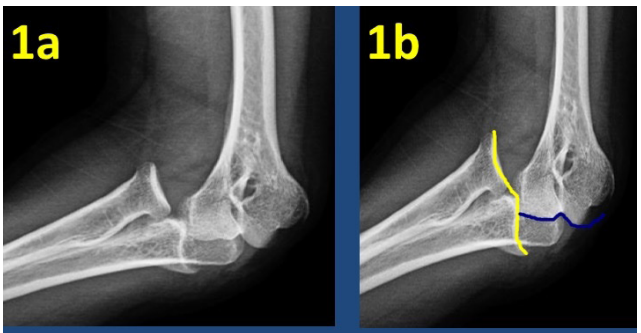

Figure 1

Figure 1. 23 years old male with elbow dislocation a- The anterior-posterior elbow radiograph b- The disruption of the 'sea wave-like sign' seen in anterior-posterior elbow radiograph (This means the elbow is dislocated)

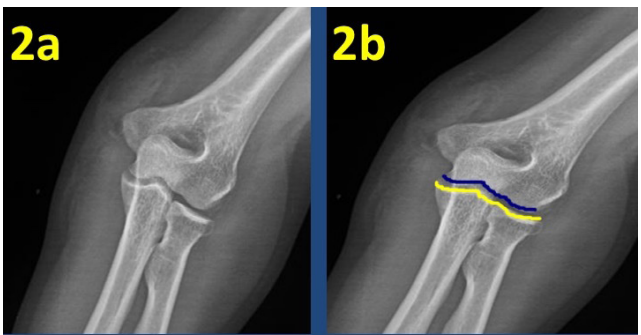

Figure 2

Figure 2. 23 years old male with reduced elbow a The anterior-posterior elbow radiograph b The colored lines indicates that 'sea wave-like sign' seen in anterior-posterior elbow radiograph (This means the elbow is reduced)

All adult patients with SED were evaluated with the same protocol. Closed reduction of the elbow with traction was done at the Emergency Department under sedation with propofol. All patients were evaluated with pre-reduction and post-reduction radiographs. A definitive diagnosis of reduction was made with post-reduction CT.

Evaluations were performed by five Orthopedic residents (Group I), five Orthopedic specialists with less than 10 years of professional experience (Group II), and five

Orthopedic specialists with more than 10 years of professional experience (Group III). They have evaluated the 12 randomly selected cases with pre-reduction and post-reduction anterior-posterior radiographs. They were requested to fill out a questionnaire including the reduction and 'sea wave-like sign'. The reduction of the elbow joint was confirmed by CT in all the randomly selected 12 cases. The observers evaluating the radiographs were blinded to the CT images and the results of the patient. Only the evaluator had access to the full sets of images and results of patients.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY, USA). Descriptive statistics for the numerical variables were expressed as the mean, standard deviation, and minimum-maximum values. Kruskal-Wallis H test was used for comparisons of three and more groups, and Wilcoxon sign test was used for pre-post comparisons. The results were evaluated within the 95% confidence interval and P <0.05 was considered as statistically significant.

RESULTS

The sensitivity, specificity, positive predictive value, and negative predictive value of the sea wave-like sign on radiography was determined by CT. As a result of 12 evaluations by each 15 observer, 180 evaluations were achieved. The sensitivity of the sea wave-like sign on radiography was 76% and specificity was 96.6%. Also, the positive predictive value of this evaluation was 99.1% and the negative predictive value was 44.6% (Table 1).

There were statistically significant differences between the groups in terms of evaluation of the reduction of the elbow joint. The correct response rates in young specialists were significantly lower than the other two groups ($p<0.05$) (Table 2).

There were no statistically significant differences between the groups in terms of evaluation of the presence of 'sea wave-like sign' ($p=0.266$) (Table 2).

All radiographs were re-evaluated by the same researchers for intra-rater reliability one month after the first evaluation. Intraclass correlation coefficients showed high intra-rater reliability.

DISCUSSION

In the present study, authors evaluated the reliability of the use of 'sea wave-like sign' in adult SED. The most important finding of the current study was that interobserver and intraobserver agreement of all examiners were high.

There is consensus in the literature about the use of conservative methods in the treatment of adult SED (3,6,9). However, the outcomes of conservative treatment are not always favorable. Schnetzke et al. emphasized the importance of initial joint stability in SED (14). Therefore, primary soft tissue repair to treat unstable elbow dislocation could be preferred (7,11,13). In the current study, authors made evaluations in 12 randomly selected cases with adult SED, which were treated conservatively.

Table 1: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Sea Wave-Like Sign

		Information Obtained by CT Images		
		Reduced	**Dislocated**	**Total**
Sea Wave-Like Sign on Radiograph	**Correct Answer**	114	1	115
	Wrong Answer	36	29	65
	Total	150	30	180

* As a result of 12 evaluations by 15 evaluators, 180 evaluations were achieved.

Table 2: The Evaluation of reduction and Sea Wave-Like Sign on Radiograph Between Groups

	Resident (n=5)	**Young Specialist (n=5)**	**Senior Specialist (n=5)**	**P**
Evaluation of reduction on radiograph	11,00	9,20	11,40	0,033
Sea wave-like sign on radiograph	10,00	8,80	9,60	0,266

*In this study, the evaluation was based on the result of 12 points.

There are many studies for the evaluation of elbow joint in direct radiography. The various criteria for evaluating the elbow joint are mentioned in the literature. These criteria are Baumann angle on AP view; hourglass sign, posterior fat bad, anterior humeral line crossing the middle of the capitellum, crossing the line drawn from the coronoid in front of the lateral condyle of the humerus, and humerocapitellar angle on lateral view (2,5,15). Since many of these criteria are aimed to evaluate fractures, the current study aimed to found new criteria for elbow dislocation in AP X-ray.

There are limited studies available in the literature, which evaluated the radiology of the elbow dislocation. Previous studies which have emphasized the importance of lateral radiography were defined some criteria about the reduction of elbow (10). There is not enough definition for evaluation of elbow dislocation on AP X-ray, except the relative articular congruity (1). Nevertheless, it is not easy to decide the reduction of the elbow joint with direct radiography. CT is often used to decide the reduction of the elbow joint. Increased radiation exposure and being not affordable are disadvantages of CT usage. The 'sea wave-like sign' may reduce the need of CT imaging in SED.

This study has several limitations. The radiographic evaluations were not compared with the clinical results. Therefore, further prospective studies are needed. This study was conducted in one single department, and the findings may not necessarily generalizable.

CONCLUSION

Sea wave-like sign can be used for evaluation in adult SED. The 'sea wave-like sign' may reduce the need for CT imaging in SED. Further prospective studies are needed to compare the results of the radiographic evaluation with the clinical results.

DECLARATIONS

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Ethical approval: The study was approved by the Institutional Ethical Committee (E-18-2446).

Availability of data and material: The data and material of the work are deposited by the corresponding author.

Authors' contributions: Design and writing: OB, writing: GO, critically revision: GO, Data Collection: BK, Data analysis: EC, revision: AD

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Electroconvulsive Therapy Before or After Initiation of Clozapine in Schizophrenia - A Retrospective Comparison for Seizure Parameters, Treatment Response and Duration of Hospitalization

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ABSTRACT

Purpose: Determining whether adjunctive electroconvulsive therapy (ECT) with clozapine leads to better treatment response and decreased length of stay for patients with schizophrenia.

Methods: Medical records of patients with schizophrenia who were treated with ECT-clozapine combination in our women's mental health inpatient clinic in a period of 5 years (between 01.02.2014 and 01.02.2019) were investigated retrospectively. Clinical Global Impression of Improvement (CGI-I) scale was used for assessing treatment response.

Results: Of the 191 cases treated with ECT, there were 8 cases of schizophrenia who were treated with ECT and concomitant clozapine (C-ECT) and 14 cases who were treated with ECT before the initiation of clozapine (ECT-B). Number of ECT sessions and duration of seizures were not significantly different for both groups ($p > 0.05$). There was good and mild response (CGI-I score of 2 and 3) in 75% of the patients (n=6) for C-ECT and 85.7% of the patients (n=12) for ECT-B. Mean CGI-I scores between the two groups were not significantly different ($p > 0.05$). Duration of hospitalization for the C-ECT group (37.7 ± 14.44 days) was shorter than the duration of hospitalization for the ECT-B group (56.0 ± 19.2 days) ($p = 0.04$). No serious adverse events were observed during the ECT sessions or during the index hospitalizations.

Conclusion: Response rate was high and similar in both of the procedures and the duration of hospitalization was shorter for C-ECT group with no significant increase in serious complicatins and adverse effects.

Key words: ECT, clozapine, schizophrenia

Şizofrenide Klozapin Başlanmasından Önce ya da Sonra EKT – Nöbet Parametreleri, Tedavi Yanıtı ve Hastanede Yatış Süresinin Retrospektif Bir Karşılaştırması

ÖZET

Amaç: Şizofreni tanılı hastalarda klozapin ile eşzamanlı olarak uygulanan elektrokonvulziv tedavinin (EKT) daha iyi tedavi yanıtı ve hastanede yatış süresinde kısalmaya neden olma olasılığını incelemek amaçlanmıştır.

Yöntemler: Kadın psikiyatri kliniğimizde 5 yıl boyunca (01.02.2014 ve 01.02.2019 arasında) yatarak tedavi gören şizofreni tanılı hastaların tıbbi kayıtları retrospektif olarak incelendi. Tedavi yanıtını değerlendirmede Klinik Global İzlem – İyileşme (KGİ-İ) ölçeği kullanılmıştı.

Bulgular: EKT ile tedavi edilmiş olan 191 olgu içinde; 8 şizofreni olgusu EKT ve eşzamanlı klozapin ile tedavi edilmiş (K-EKT) ve 14 olguya ise önce EKT uygulanmış, sonrasında klozapin tedavisine başlanmıştı (EKT-Ö). İki grup arasında EKT seans sayıları ve nöbet süreleri açısından anlamlı fark yoktu ($p > 0.05$). EKT'ye iyi ya da hafif yanıt oranının (KGİ-İ: 2 ya da 3), K-EKT grubunda %75 (n=6); EKT-Ö grubunda ise %85,7 (n=12) olduğu görüldü. Ortalama KGİ-İ skorları arasında gruplar arasında anlamlı fark yoktu ($p > 0.05$). K-EKT grubunun hastanede yatış süresi ($37,7 \pm 14,44$ gün), EKT-Ö grubundan ($56,0 \pm 19,2$ gün) daha kısaydı ($p = 0,04$). EKT seansları sırasında ya da yatışlar süresince ciddi yan etki görülmedi.

Sonuç: Her iki uygulamada da tedaviye iyi yanıt yüksek orandaydı ve uygulamalar arasında anlamlı fark yoktu. EKT ile eşzamanlı klozapin uygulamasının hastanede yatış süresini anlamlı oranda kısaltırken ciddi komplikasyonlar ve yan etkilerde artışına neden olmadığı görüldü.

Anahtar kelimeler: EKT, klozapin, şizofreni

The first electroconvulsive therapy (ECT) device was invented by Ugo Cerletti and Lucio Bini in 1938 and was used in the treatment of a patient with the diagnosis of schizophrenia (1).

Today, there are variations in the rates of ECT use for different psychiatric disorders between countries. In Europe and North America, ECT is generally used for depression and affective disorders (2). There can be changes in the rates of ECT use between years, largely because of changing attitudes of psychiatrists towards ECT (3). Bipolar disorder (32.8%) and schizophrenia (29.1%) were the two of the most frequent diagnoses for the patients who were treated with ECT in our hospital as it was reported in a study documenting the 3 years of the practice of ECT (4).

Clozapine is the treatment of choice in refractory schizophrenia (5). ECT is the treatment indicated for refractory conditions, it is markedly effective as an acute treatment of clozapine-refractory schizophrenia, when used as an augmentation strategy (6). Despite the evidence favoring ECT augmentation of pharmacotherapy, particularly clozapine, in treatment resistant schizophrenia (7,8), because of the inadequacy of studies in this field; ECT finds different places in treatment guidelines: American Psychiatric Association (APA) recommends ECT in treatment resistance since 2008, but National Institute for Health and Care Excellence Guidelines (NICE) still limits the recommendation only to the cases where catatonia accompanies (5,9). In addition to the treatment recommendations for schizophrenia that suggest the use of ECT in catatonia (10),there are also views that suggest ECT as an effective option in treatment resistant schizophrenia (11) and there is beneficial additive effect of ECT-clozapine combination (12). According to a Cochrane systematic review; especially when rapid symptom reduction is needed and response to medication is limited; ECT combined with antipsychotics is a suitable option (13) and ECT is expected to be effective in clozapine resistance (14).

Until recently, our knowledge about ECT with concomitant clozapine treatment was based on case reports and case series, but there has been recent studies including a controlled study of 18 patients reporting improvement in positive symptoms, and a prospective randomized controlled study of 39 patients which reports %50 positive response increased the amount of evidence (15,16).

Aims

The aim of this retrospective study was to investigate the clinical consequences of ECT augmentation of clozapine and discover the differences between ECT with concomitant clozapine (C-ECT) and ECT before the initiation of clozapine (ECT-B).

The main hypothesis was that adjuvant ECT with clozapine would lead to better acute treatment response and fewer days in hospital without significant increase in medical complications.

METHOD

Study design

The study sample consisted of the inpatients with the diagnosis of schizophrenia who were treated with both ECT and clozapine because of treatment resistance in a period of 5 years (between 01.02.2014 – 01.02.2019) in the women's mental health inpatient clinic of our hospital. The medical records of the patients who received ECT while already using clozapine were compared with the patients who were started clozapine after ECT sessions were over. Patients with serious medical comorbidity and mental retardation were excluded because of the possibility of confounding effect.

Patient selection and data sources

Our clinic is an inpatient tertiary care center for psychiatric referrals from the region. Indications for inpatient psychiatric care were risk of suicide, risk of homicide and inability to care for oneself. There were 33 beds in the inpatient unit that the retrospective data was derived, the unit was part of the female psychiatry clinics of the research and training hospital for psychiatric disorders. During the survey period (February 2014- February 2019), the total number of psychiatric hospitalizations to the unit was 2738, and during this period 191 female patients received ECT. Two cases with serious medical comorbidity (gastric carcinoma and chronic renal failure) and two cases with mental retardation were excluded. Regarding the patients with the diagnosis of schizophrenia; there were 8 cases who received ECT concomitant with clozapine (C-ECT) and 14 cases who were treated with ECT before the initiation of clozapine (ECT-B) in our study. The diagnosis were made according to Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition (DSM-5) criteria. Treatment resistance for schizophrenia was defined as resistance to two or more antipsychotics and duration of illness more than two years. The diagnoses and the presence of treatment resistance were confirmed by two different psychiatrists

of the clinic during the hospitalization (17). ECT augmentation of clozapine was used when there were at least moderate psychotic symptoms that prevented discharge from hospital despite continuous clozapine treatment.

Electroconvulsive therapy (ECT)

Since 2006, ECT has been administered with anesthesia in our hospital (18).Written informed consent were obtained from the patients themselves, or from their legal representatives as part of ECT regulations in our country. In emergency situations such as refusal of oral intake resulting in malnutrition or severe suicidal risk, when there is no legal representative available, ECT may be performed by the consent of two psychiatrists. ECT with anesthetic and muscle relaxant was applied with a frequency of thrice a week. Propophol (0,75-1mg/kg) was used for anesthesia and succinylcholine (0.5mg/kg) was used as muscle relaxant. ECT was applied with Thymatron System IV integrated ECT instrument– a brief-pulse-square-wave ECT device (Somatics, LCC, Lake Buff, Ill). with bilateral electrode placement. Half-age method was used in determining initial stimulus intensity. When the patient was using clozapine, initially the stimulus dose was decreased 10% because of the possible decrease in seizure threshold. If there was history of recent use of benzodiazepine or antiepileptic agents, the stimulus dose was increased 10%. Shorter than 25 seconds was considered inadequate seizure, longer than 120 seconds was considered as a prolonged seizure. Restimulation was performed with a higher intensity if the seizure lasted less than 20 seconds. When the duration of seizure was as low as 25-30 seconds, the stimulus dose was increased 10% in subsequent ECT sessions. Ventilation was applied with face-mask. Oxygenation was continuously monitored with pulse oximetry. Noninvasive positive pressure ventilation with 100% oxygen was used for assisting respiration. All the patients were also monitored with electrocardiogram (ECG), electromyography (EMG) and electroencephalogram (EEG). The indication for adjuvant ECT with clozapine was unresponsiveness to other treatments.

Instruments

Socio-demographic data form

There were three kinds of medical records; the electronical hospital records, inpatient clinical forms and ECT Unit data charts. All the relevant clinical information from previously recorded reports and charts were condensed in the data form which was prepared by the researchers.

Clinical Global Impression of Improvement Scale

Treatment response was determined with psychiatric evaluation and recorded with the Clinical Global Impression of Improvement (CGI-I) scale as a part of routine evaluation of all the patients receiving ECT. It is a 7-point scale (0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). It is considered a robust and quick measure of efficacy if the clinician knows the patient well and is commonly used for measuring the effect of pharmacotherapy (19) and ECT (20). CGI-I scores were determined by the treating clinicians of the patients during the hospitalizations and were recorded in the medical files.

Statistical Analysis

IBM SPSS Statistics 21.0 (IBM Corp., Released 2012. IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY, USA) was used in statistical analysis. For the continuous variables, descriptive statistics in mean and standard deviation were calculated. Median values were also presented when considered informative. For categorical variables, frequencies and percentages were presented. Since the data distribution from ECT with Clozapine Treatment (C-ECT) and ECT Before Initiation of Clozapine (ECT-B) groups were not normal, comparisons were made with Mann-Whitney U Test.

Ethics

The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or compatible ethical standards. The study was approved by the ethics committee of the institution (18.01.2019-2446).

RESULTS

Socio-demographic and clinical findings

There were 8 cases in the C-ECT group and 14 cases in the ECT-B group. Mean age of the C-ECT group was 37.1 ± 9.90, and 40.8 ± 10.15 in the ECT-B group. Mean duration of illness was 12.7 ± 7.28 years in C-ECT group and 12.6 ± 8.06 years in ECT-B group. Mean number of previous hospitalizations for patients in C-ECT group was 3.8 ± 2.74, it was 3.5 ± 2.53 in ECT-B group. Clinical features of the patients are presented in Table 1.

Table 1. Clinical Features and Medications of the Patient Groups		
Descriptive Features	**C-ECT** (n=8) Mean ± SD	**ECT-B** (n=14) Mean ± SD
Age	37.1 ± 9.90	40.8 ± 10.15
Duration of illness (years)	12.7 ± 7.28	12.6 ± 8.06
Previous hospitalizations	3.8 ± 2.74	3.5 ± 2.53
Weight (kg)	76.3 ± 19.55	69.2 ± 12.49
Height (cm)	160.3 ± 7.26	161.6 ± 6.34
Pseudocholinesterase level	6568 ± 3745.9	6521 ± 2167.0
Features of the first ECT session		
Pulse rate	98.2 ± 24.13	85.8 ± 16.37
Propophol dose (mg)	60.0 ± 13.09	57.8 ± 14.23
Succinylcholine dose (mg)	34.3 ± 6.23	30.3 ± 6.34
Energy in the first session	18.7 ± 6.40	23.5 ± 7.18
Seizure duration in the first session in seconds (EEG)	28.3 ± 27.75	48.0 ± 21.08
Clozapine Dosing		
Clozapine dose during ECT (mg)	312 ± 132.9	-0-
Clozapine dose at the end of hospitalization (mg)	425 ± 116.4	317 ± 155
Other Medications	**C-ECT** N = number of cases Mean Dose ± SD (mg)	**ECT-B** N= number of cases Mean Dose ± SD (mg)
Theophylline	N=2 120 ± 0	N=1 120 ± 0
Remifentanyl	N=2 75 ± 7.0	N=1 50 ± 0
Quetiapine	N=2 450 ± 70.7	N=8 312 ± 188.5
Haloperidol	N=1 20 ± 0	N=9 20 ± 0
Amisulpride	N=2 600 ± 282.8	N=2 1000 ± 282.8
Chlorpromazine	N=1 50 ± 0	N=2 37 ± 17.6
Olanzapine	N=1 10 ± 0	N=1 10 ± 0
Lorazepam	N=1 2.0 ± 0	N=1 2.5 ± 0
C-ECT: ECT with Clozapine Treatment, ECT-B: ECT Before Initiation of Clozapine		

The choice of anesthetic agent was propophol, mean dose was 60.0 ± 13.09 mg in C-ECT group and 57.8 ± 14.23 mg in ECT-B group. Succinylcholine was used for all patients as muscle relaxant, mean dose being 34.3 ± 6.23 mg in C-ECT group, 30.3 ± 6.34 mg in ECT-B group. Clozapine dose during ECT was 312 ± 132.9 mg in C-ECT group. Patients in the ECT-B group were not using clozapine during the ECT sessions; for these patients, ECT was administered before the initiation of clozapine treatment. Clozapine doses at the time of discharge from hospital were 425 ± 116.4 for C-ECT group and 317 ± 155 for ECT-B group. The clozapine doses at discharge were higher for the C-ECT group, but the difference was not significant (p=0.083). Energy, seizure duration and other features of the first ECT session and clozapine doses are also presented in Table 1.

Medication

When the duration of seizure shortened significantly,in line with the institutional protocols of the ECT center, theophylline was given intravenously with the dose of 120 mg to two of the patients in C-ECT group and to one of the patients in ECT- B group 15 minutes before the procedure for decreasing the seizure threshold. When it was not appropriate to use theophylline because of tachycardia, remifentanyl with a dose of 1 mg / kg was added to the pre-ECT medications by the anesthesiologist with the aim of decreasing the dose of propophol to mitigate its effect on seizure threshold (Propophol increases the seizure threshold and addition of remifentanyl enables us to use propophol in half-dose). 2 patients in the C-ECT group

and one patient in ECT-B group were given remifentanyl. Patients were also given additional psychopharmacological agents during the hospitalization. The use of other medications combined with clozapine were given in Table 1.

Remission and response rates

Clinical outcome was scored with CGI-I scale. There were 2 patients in the C-ECT group who did not improve and 6 patients (75 %) improved at least minimally. 7 (50.0 %) patients significantly improved (CGI-I = 2). There were also 2 patients in the ECT-B group who did not improve and 12 patients (85.7%) improved at least minimally. CGI-I results of the groups are presented in Table 2.

Medical Complications During ECT

Prolonged confusion was the reason for premature cessation of ECT in two patients in the ECT-B group. The other complications that occurred during the ECT sessions did not prevent completion of the course of ECT. Confusion was observed in 3 patients in the ECT-B group. Inefficient seizures were observed in 5 patients in the C-ECT group and 6 patients in the ECT-B group. No deaths occurred during the ECT sessions or during the index hospitalizations and no severe adverse event such as fractures or cardiac arrest was observed. There were no prolonged seizures and significant increase in complications (p> 0.05). Medical complications during ECT sessions are presented in Table 2.

Table 2. Clinical Global Improvement and Medical Complications

Clinical Global Impression of Improvement (CGI-I)	**C-ECT** (n=8) N (%)	**ECT-B** (n=14) N (%)
Completely improved (CGI-I = 1)	0	0
Significantly improved (CGI-I = 2)	3 (37.5)	7 (50.0)
Minimally improved (CGI-I = 3)	3 (37.5)	5 (35.7)
No change (CGI-I = 4)	2 (25.0)	2 (14.3)
Premature ending due to medical complications	0	2*
Medical Complications (Pearson Chi-Square = 2.112, p = 0.348#)		
None	3	5
Confusion	0	3
Inefficient seizure	5	6

C-ECT: ECT with Clozapine Treatment, ECT-B: ECT Before Initiation of Clozapine, *confusion, #:4 cells (66,7%) have expected count less than 5. The minimum expected count is 1,09.

Comparisons of Distinctive Treatment Outcomes

Mean number of ECT was 8.7 ± 3.24 sessions with a median of 8 in C-ECT group and 9.0 ± 2.63 sessions with a median of 9 sessions in ECT-B group; similar in the two groups (p > 0.05). Mean seizure duration was 42.5 ± 21.17 seconds in C-ECT group and 39.7 ± 13.8 seconds in ECT-B group in EEG and it was 30.7 ± 9.41 seconds in C-ECT group, 29.8 ± 9.96 in the ECT-B group in EMG; they were also similar in duration (p > 0.05).

Mean CGI-I scores were 2.8 ± 0.83 with a median of 3 in C-ECT group and 2.6 ± 0.74 with a median of 2 in ECT-B group. There was no significant difference between CGI-I scores (p > 0.05).

Mean duration of hospitalization was 37.7 ± 14.44 days (median: 40 days) in the C-ECT group and it was significantly shorter from the mean duration of hospitalization of the ECT-B group which was 56.0 ± 19.2 days (median: 51 days) (Z = - 2.048, p = 0.042). Comparisons of treatment outcomes are presented in Table 3.

DISCUSSION

Duration of hospitalization was significantly shorter in the C-ECT group in our study. As we know from the previous reports, mean duration of hospitalization for the patients who were not treated with ECT was 22 days and mean duration of hospital stay for the patients who were treated with ECT with different diagnoses was 33 days in our hospital (4). Duration of hospitalization for the ECT-B group was significantly longer when it was compared to the C-ECT group or the previously reported mean durations of hospitalizations. The time needed for titration of clozapine from zero to a therapeutic dose was one of the main reasons for longer duration of hospitalization in the ECT-B group. Such an extra duration of hospitalization in the C-ECT group were not necessary because they were already using clozapine and they continued to use clozapine during the ECT procedure.

Table 3. Comparisons of Treatment Outcomes				
	C-ECT (n=8) Mean ± SD	**ECT-B** (n=14) Mean ± SD	**Z**	**p**
Number of ECT sessions	8.7 ± 3.24 (median=8)	9.0 ± 2.63 (median=9)	-0.415	0.714
Seizure duration in seconds (EEG)	42.5 ± 21.17 (median=34)	39.7 ± 13.80 (median=39)	-0.137	0.920
Seizure duration in seconds (EMG)	30.7 ± 9.41 (median=28)	29.8 ± 9.96 (median=28)	-0.239	0.815
CGI-I	2.8 ± 0.83 (median=3)	2.6 ± 0.74 (median=2)	-0.665	0.570
Duration of hospitalization in days	37.7 ± 14.44 (median=40)	56.0 ± 19.20 (median=51)	-2.048	**0.042**
C-ECT: ECT with Clozapine Treatment, ECT-B: ECT Before Initiation of Clozapine				

Inpatient treatment is one of the costliest practices in medical expenditures (21). In addition to the economic costs of a long hospital stay, being hospitalized in a closed psychiatric ward, usually is not a pleasant experience as perceived by the patients. Longer days in hospital are also associated with negative consequences such as increased stigmatization (22).

To date, no life-threatening side-effects or deaths has been reported in the literature for the combination of ECT and clozapine. Preliminary data from nonrandomized open-label studies suggest that addition of ECT may be an effective alternative for patients with clozapine-resistant symptoms (15). Although available data indicate that ECT is an effective acute treatment for schizophrenia, including treatment-resistant cases, the number of controlled studies is still small, and clinicians are less inclined to recommend ECT for this population (17). In our study, there was no significant difference between C-ECT and ECT-B groups and the response rates were high in both groups. For psychotic disorders, women have higher ECT response and remission rates as reported previously in the literature (23). A previous naturalistic study from a different center in our country also reported high response rates, which the researchers interpreted to be due to careful selection of possible good responders for ECT by clinicians as they conclude (24).

Clozapine doses during ECT were in the therapeutic range (target dose for female non-smokers = 250 mg/day, female-smokers = 450 mg/day). Clozapine doses at the time of discharge were also higher in C-ECT group, this was probably due to the fact that clozapine initiation time was earlier in these patients. Although duration of illness was similar in both groups, treatment resistance could also be a factor warranting higher doses of clozapine in the C-ECT group.

Seizure durations were not different in the C-ECT and ECT-B groups. Although clozapine decreases seizure threshold, we did not encounter any prolonged seizures. Instead, there were short and ineffective seizures in 5 sessions during ECT with clozapine. Our institutional protocol that recommended decreasing the first stimulus dose 10% for patients using concomitant clozapine during ECT could possibly be the reason for the seizure durations' being similar across the groups. Succinylcholine and propophol were the principal medications for modified ECT procedure. Propophol which we have used in all ECT sessions is an agent that increases seizure threshold and this could be another reason that we did not observe prolonged seizures.

Addition of theophylline or remifentanyl were needed to ensure effective seizures in 6 patients in the C-ECT group. Inefficient seizures were also observed in patients in the ECT-B group and this was surpassed by increasing the stimulus dose and addition of theophylline or remifentanyl.

Number of ECT sessions were not different across C-ECT and ECT-B groups in our study, with a median of eight and nine sessions respectively. These results were in line with previous studies from our institution reporting mean number of ECT sessions as 7.89 ± 2.86 (4). Courses of adjuvant ECT ranging from six to ten sessions were previously reported to be effective in schizophrenia, but the number of sessions varies in different studies (13). When ECT was used with the purpose of clozapine augmentation in treatment resistant schizophrenia, it was also suggested that

the number of sessions should be more compared to other indications of ECT (18).

The major limitation of our study was that it was not possible to randomize patients to their respective treatment groups because our study was a retrospective chart review. The relatively small sample size and the sample's consisting of only female patients were also limitations. While approaching resistance to clozapine treatment, the serum levels of clozapine were not detected in our study and there could be patients who were resistant to clozapine because they were rapid metabolizers. Detection of serum levels of clozapine was not a routinely available test in our hospital, but we recommend considering clozapine serum levels for future studies and clinical decisions.

Since this was a naturalistic retrospective study, the patients were also given other medications with clozapine. Randomized controlled trials are needed in this topic for overcoming this limitation.

Although the complications in the C-ECT and ECT-B groups were similar in frequency in our study, it is worth mentioning that there can be other complications of ECT and clozapine treatment as we know from the literature: The most serious complication reported in the literature until today is pulmonary emboli during the adjunctive ECT with clozapine, but it has been difficult to claim a cause and effect relationship with the procedure, because there is only one case (25). Supraventricular tachycardia (26), atrial fibrillation (27), Takotsubo cardiomyopathy (28) and aspiration risk under general anesthesia (29) were other serious medical consequences reported in the literature. Prolonged seizures, postictal cognitive dysfunction, tachycardia and fluctuations in blood pressure were other reported side effects of adjunctive ECT with clozapine.

We did not find any significant increase in complications in clozapine-ECT combination, moreover; there is a chance that it decreases the time spent in the inpatient unit. We suggest that when ECT is indicated for a patient using clozapine, instead of cessation of clozapine treatment before ECT, continuing clozapine treatment and augmenting clozapine with concomitant ECT is a favorable option. This may decrease the days spent in hospital without significant increase in medical complications in patients with schizophrenia. Studies with larger sample sizes in both genders would enhance our knowledge in combination of clozapine and ECT.

Conflict of Interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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The Effect of Clinical, Laboratory Findings and Parenchymal Infiltration Features on the Diameter of the Main Pulmonary Artery in COVID-19 Pneumonia

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ABSTRACT

Purpose: The main pulmonary artery diameter is an indirect indicator of the pulmonary vascular bed resistance. In this study, it was aimed to reveal the parameters that are associated with respiratory distress by evaluating the parameters affecting the diameter of the main pulmonary artery in patients diagnosed with COVID-19 pneumonia.

Methods: The relationship the presence of a comorbidity, clinical findings, laboratory values, pulmonary infiltration features, and main pulmonary artery diameter (MPAD) was statistically evaluated.

Results: When MPAD 27.5 mm was considered as enlargement; it was significantly wider in smokers in COVID-19 pneumonia ($p<0.05$). It was statistically shown that there was no association with diabetes, hypertension, asthma, or COPD and MPAD ($p>0.05$). It was observed that MPAD was associated with shortness of breath ($p=0.039$; $p<0.05$) but not with cough and fever ($p>0.05$). Also, it was found that MPAD was significantly wider in cases with high CRP and LDH values ($p=0.008$; $p<0.01$, $p=0.011$; $p<0.05$, respectively). While MPAD did not differ significantly in those with ground-glass infiltration; MPAD was significantly larger in those with infiltration in the form of crazy-paving or consolidation ($p<0.05$). While there was no significant variation in MPAD in those with periferobasal involvement; MPAD was significantly wider in cases with central or mixed infiltration ($p<0.05$).

Conclusion: It is possible to indirectly predict respiratory distress in COVID-19 patients by measuring MPAD, which is associated with respiratory distress. CRP and LDH values, central infiltration in the pattern of crazy-paving or consolidation are related with increased MPAD in COVID-19 pneumonia.

Keywords: COVID-19, SARS-CoV-2, respiratory distress, main pulmonary artery diameter, chest CT, crazy-paving, ground-glass opacity

COVID-19 Pnömonisinde Klinik, Laboratuvar Bulguları ve Parankimal İnfiltrasyon Özelliklerinin Ana Pulmoner Arter Çapına Etkisi

ÖZET

Amaç: Ana pulmoner arter çapı, pulmoner vasküler yatak direncinin dolaylı bir göstergesidir. Bu çalışmada COVID-19 pnömonili olgularda ana pulmoner arter çapını etkileyen parametreler değerlendirilerek solunum distresi ile hangi parametrelerin ilişkili olduğunu ortaya çıkarmak amaçlanmıştır.

Yöntem: Komorbid hastalıklar, klinik bulgular, laboratuvar değerleri, pulmoner infiltrasyon özellikleri ve ana pulmoner arter çapı (APAÇ) arasındaki ilişki istatistiksel olarak değerlendirildi.

Bulgular: APAÇ>27,5 mm genişleme olarak kabul edildiğinde; COVID-19 pnömonisinde APAÇ sigara içenlerde anlamlı olarak daha genişti ($p<0.05$). Diyabet, hipertansiyon, astım veya KOAH ile APAÇ arasında anlamlı ilişki saptanmadı ($p> 0.05$). APAÇ'ın nefes darlığı ile ilişkili olduğu ($p=0,039$; $p<0,05$) ancak öksürük ve ateşle ilişkili olmadığı ($p>0,05$) görüldü. Ayrıca CRP ve LDH değerleri yüksek olan olgularda APAÇ'ın anlamlı olarak daha geniş olduğu saptandı (sırasıyla $p=0,008$; $p<0,01$, $p=0,011$; $p<0,05$). APAÇ, buzlu cam formunda parankimal infiltrasyonu olanlarda anlamlı farklılık göstermezken; crazy-paving (kaldırım taşı) veya konsolidasyon şeklinde infiltrasyonu olanlarda APAÇ anlamlı olarak daha genişti ($p <0.05$). Periferobazal dağılım gösteren infiltrasyonu olanlarda APAÇ'ta anlamlı bir artış olmamakla birlikte; santral ve yaygın infiltrasyonu olan olgularda APAÇ anlamlı olarak daha genişti ($p<0.05$).

Sonuç: Solunum distresi ile ilişkili olan APAÇ ölçülerek, COVID-19 pnömonili olgularda solunum distresini dolaylı yoldan radyolojik olarak tahmin etmek mümkündür. COVID-19 pnömonisinde CRP ve LDH değerleri, crazy-paving veya konsolidasyon paterninde santral ve yaygın infiltrasyon artmış APAÇ ile ilişkilidir.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, solunum distresi, ana pulmoner arter çapı, toraks BT, crazy-paving, buzlu

The pandemic caused by the SARS-CoV-2 virus has infected 236 million people as of April 2021, causing 4.8 million deaths worldwide (1). The clinical symptoms are severe and a result of diffuse alveolar damage caused by affecting the lower respiratory tract (2). Respiratory distress is a common cause of death in patients infected with the virus (2,3). However, alveolar damage and impaired pulmonary oxygenation are responsible for the respiratory distress experienced in many patients with severe disease (2,3). In this retrospective study, we evaluated the parameters that were associated with the increase in main pulmonary artery diameter (MPAD), which is an indirect indicator of the resistance created by the impaired ventilation / perfusion balance in the pulmonary vascular bed in COVID-19 pneumonia cases. Thus, we aimed to predict whether the patient will have respiratory distress by looking at the diameter of MPAD in patients diagnosed with COVID-19 pneumonia, and to help clinicians in terms of early treatment or hospitalization.

MATERIAL AND METHODS

Local institutional review board approval was obtained for this retrospective study (2020-05/28), and informed consent forms were obtained before CT acquisition.

Study population: The study was performed retrospectively by evaluating the images of patients who applied to our clinic with suspected COVID-19 and underwent low-dose non-contrasted chest computerized tomography (CT) between March 2020-March 2021.

Inclusion criteria: Cases with radiologically or PCR-proven COVID-19 infection and CT performed in our hospital due to COVID-19 were included in the study.

Exclusion criteria: Patients with widespread organizing pneumonia or adult respiratory distress syndrome (ARDS) pattern, patients with pleural effusion, suspicious lung mass for malignancy, previous lung operation history, pulmonary thromboembolism, patients receiving radiotherapy to the chest area, and patients with a history of rheumatologic disease were excluded from the study.

Imaging methods: All CT scans were done with Siemens Somatom Sensation-Syngo CT 2009 device using a low-dose non-contrast CT protocol. Patients were scanned in the supine position during deep inspiration. The acquisition parameters were standardized as; tube voltage:140 kV, tube current:40 mA, pitch:1,4, FOV:455 mm, slice thickness:64x0,6 mm. The isolation rules were applied during and after the scanning had complied. All measurements were calculated by an experienced radiologist in chest CT.

Image analysis: The main pulmonary artery diameter (MPAD) of SARS-CoV-2 PCR (+) cases admitted to the hospital were measured by a radiologist experienced in chest CT with standardized measurement locations and techniques. MPAD whether equal and above 27.5 mm was accepted as enlargement (4). The patient's chronic diseases (diabetes, hypertension, asthma, chronic obstructive pulmonary disease (COPD), other diseases), smoking history, patient's laboratory parameters (lymphocyte count, Neutrophil / Lymphocyte ratio (N/L), D-Dimer, lactate dehydrogenase (LDH), Ferritin, Procalcitonin), dominant symptoms (high fever, shortness of breath/dyspnea, cough), lung parenchyma infiltration features (dominant infiltration pattern:ground-glass opacity, crazy-paving or consolidation, involved lobe, distribution of involvement: periferobasal, central or mixed) due to COVID-19 pneumonia was statistically evaluated according to the MPAD variability. It was evaluated that which variables associated with MPAD in the study.

Measurement methods: In the study, the MPAD were measured in all cases. The widest diameter perpendicular to the long axis of the MPAD was measured with computer calipers at the level of the pulmonary artery (PA) bifurcation. (Figure 1) (5).

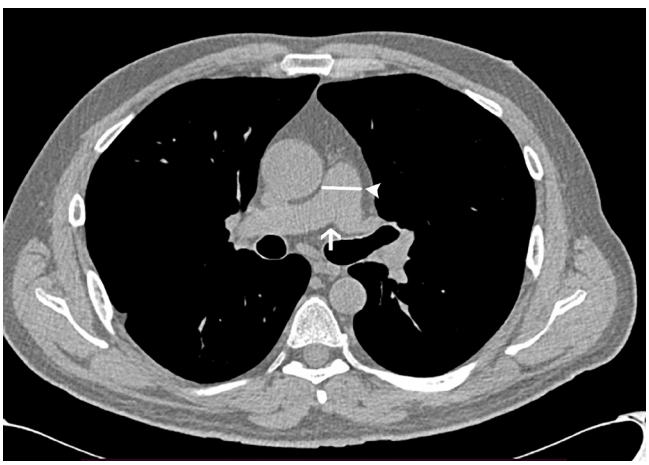

Figure 1. Demonstration of MPAD's measurement method. The widest diameter perpendicular to the long axis of the MPAD (arrow head) was measured with computer calipers at the level of the pulmonary artery (PA) bifurcation (arrow).

Statistical analysis: Statistical analysis: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), Pearson chi-square test, Fisher's Exact test and Fisher Freeman Halton test were used for comparison of qualitative data. Significance was evaluated at p <0.05 levels.

RESULTS

A total of 102 cases were included in the study. Of these 102 cases, 71.6% (n=73) were male, 28.4% (n=29) were female, and the mean age was 48.62 ± 14.42 (19-94). The rates of diabetes, hypertension, asthma, COPD, and other diseases did not show significant difference according to the presence of MPAD enlargement (p>0.05). The smoking rate was found to be significantly higher in patients with enlargement of the MPAD compared to those without (p=0.044;p<0.05) (Table 1). The odds ratio of MPAD enlargement in smokers was 3,500 times more compared to nonsmokers (CI 95%:1,138-10,764). When the relationship between symptoms and MPAD was evaluated; there was no significant relationship between fever and cough with MPAD (p>0.05). However, MPAD was found to be significantly wider in patients with dyspnea (p=0.039; p <0.05) (Table 1).

Table 1: Relationship between MPAD enlargement and comorbid diseases /symptoms

	MPAD enlargement		p
	(+)≥27.5 mm	(-)<27.5 mm	
Diabetes mellitus	3 (16.7)	9 (10.7)	[b]**0.440**
Hypertension	4 (22.2)	16 (19.0)	[b]**0.749**
Asthma	1 (5.6)	3 (3.6)	[b]**0.546**
COPD	0 (0.0)	10 (11.9)	[b]**0.202**
Smoking	7 (41.2)	14 (16.7)	[b]**0.044***
Other Diseases	2 (11.1)	2 (2.4)	[b]**0.142**
Fever	12 (66.7)	35 (41.7)	[a]**0.053**
Dyspnea	7 (38.9)	12 (14.3)	[b]**0.039***
Cough	16 (88.9)	56 (66.7)	[a]**0.060**

[b]Fisher'sExact Test *p<0.05

When the relationship between laboratory findings and MPAD enlargement was evaluated, no statistically significant difference was found between low lymphocytes count and N/L ratio over 3 (p> 0.05). No statistically significant difference was found between D-dimer, Ferritin and Procalcitonin and the enlargement of MPAD (p>0.05). In patients with MPAD enlargement, CRP and LDH values were found to be significantly higher than those without (p=0,008; p<0,01, p=0,011; p<0,05, respectively) (Table 2).

When MPADs were evaluated according to the infiltration pattern and distribution due to COVID-19 pneumonia; it was observed that there was no significant vascular enlargement in patients with ground-glass infiltration (p>0.05), but it was significantly enlarged in patients with infiltration in the form of crazy-paving or consolidation (p=0.003; p<0.01). While MPAD was enlarged in patients with right middle lobe and left upper lobe involvement, no statistically significant difference was found in the case of infiltration of other lobes (p=0,017; p<0,05, p=0,029; p<0,05, p>0,05, respectively) (Figure 2) (Table 3).

DISCUSSION

It is known that the SARS-CoV-2 virus enters the cell by binding to the angiotensin converting enzyme-2 (ACE-2) receptors on the cell surface (6). Since the respiratory tract epithelium is rich with ACE receptors, especially upper respiratory system involvement is observed in the majority of patients (2). In case of underlying facilitating factors such as advanced age, presence of a comorbid disease, immunodeficiency, the cellular damage caused by the virus also increases (7). This situation appears as diffuse alveolar damage in the lungs that can be radiologically visualized as ground-glass opacity, which turns into a cobblestone (crazy-paving) or consolidation pattern in advanced stages (8). In case of severe destruction of the alveoli, the alveolar oxygenation disruption also causes vasoconstriction in the pulmonary vascular bed with the effect of local inflammatory cytokines (2,9). It may cause an increase in the pressure of the intrapulmonary arteries, leading to dilatation in the diameter of the main pulmonary artery. Ventilation to perfusion balance is also disturbed, reducing blood oxygenation (10). Clinically, it causes complaints of dyspnea and respiratory distress in patients that may require oxygen support. In this study, the relationship between clinical, laboratory, and radiological findings in COVID-19 pneumonia and pulmonary artery diameter was evaluated, and whether it was associated with possible virus-related pulmonary hypertension and respiratory distress experienced in the disease. According to the study, it was observed that MPAD was significantly wider in smokers and patients with dyspnea, patients with high CRP and LDH values, and cases with central or widespread involvement in the form of crazy-paving or consolidation.

Table 2: Relationship Between MPAD Enlargement and Laboratory Findings				
		MPAD enlargement		P
		(+)≥27.5 mm	(-)<27.5 mm	
Lymphopenia 10^3/uL	**(1.3 - 3.76)**	9 (50.0)	22 (41.5)	[a]**0.530**
High N/L	**>3**	8 (47.1)	18 (34.0)	[a]**0.331**
CRP (<0.5) mg/dL	**Normal**	1 (5.9)	20 (40.8)	[a]**0.008****
	High	16 (94.1)	29 (59.2)	
D-dimer (<0.5) mg/L	**Normal**	3 (30.0)	2 (12.5)	[b]**0.340**
	High	7 (70.0)	14 (87.5)	
LDH (120-246) IU/L	**Normal**	9 (50.0)	69 (82.1)	[b]**0.011***
	High	9 (50.0)	15 (17.9)	
Ferritin (10 - 291) ng/L	**Normal**	0 (0.0)	5 (26.3)	[b]**0.128**
	High	12 (100.0)	14 (73.7)	
Procalsitonin (<0.15) ng/mL	**Normal**	4 (40.0)	5 (26.3)	[b]**0.675**
	High	6 (60.0)	14 (73.7)	

[a]PearsonChi-Square Test [b]Fisher'sExact Test *p<0.05 **p<0.01

Table 3: Relationships between MPAD enlargement and parenchymal involvement pattern/ distribution				
		MPAD enlargement		P
		(+)≥27.5 mm	(-)<27.5 mm	
Ground-Glass opacity		18 (100.0)	79 (94.0)	[b]**0.583**
Crazy-paving- Consolidation		11 (61.1)	21 (25.0)	[a]**0.003****
Right Upper Lobe		14 (77.8)	43 (54.4)	[b]**0.110**
Left Upper Lobe		14 (77.8)	39 (49.4)	[a]**0.029***
Right Middle Lobe		10 (55.6)	21 (26.6)	[a]**0.017***
Right Lower Lobe		17 (94.4)	63 (79.7)	[b]**0.183**
Left Lower Lobe		16 (88.9)	62 (78.5)	[b]**0.512**
Distrubition	**Peripherobasal**	3 (16.7)	39 (49.4)	[a]**0.212**
	Central- Mixt	15 (83.3)	32 (40.5)	[a]**0.004****

aPearson Chi-Square Test bFisher'sExact Test dFisher Freeman Halton Test
*p<0.05 **p<0.01

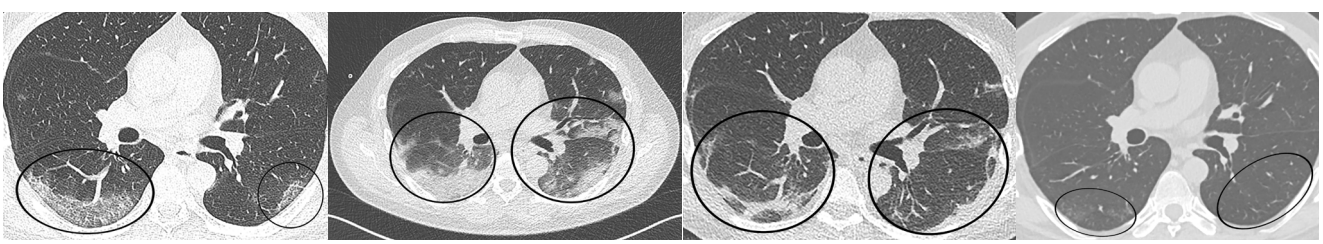

Figure 2. In Fig 2a, infiltration pattern as ground-glass opacities accompanying crazy-paving pattern distributed peripherally (circles) in the both lower lobe is seen (04.11.2020). In 2b, it is seen that the infiltration pattern turns into consolidation and the infiltration areas (circles) increase in the progression stage of the disease (10.11.2020). In Fig 2c, it is shown that in the regression phase of the disease, infiltration areas have been replaced by fibrotic band formations (circles) (17.11.2020). In Fig 2d, it is seen that all infiltrations regress almost completely, leaving their place to residual ground glass opacities (circles) (26.01.2020).

No relationship was found between MPAD and fever, which is one of the main symptoms of the disease.It can be thought that the inflammatory cytokines such as IL-1 and IL-6, which are primarily responsible for fever, can reduce pulmonary vascular resistance by vasodilator effect and do not cause a significant change in MPAD (11,12). No relationship was found between MPAD and low lymphocyte count and high N/L ratio, which are considered as pathognomonic laboratory findings of the disease. The reason for this situation may be that the immunological battle with the virus is at the intravascular level rather than the pulmonary interstitial area. However, the relationship between CRP, which is considered as an indicator of the degree of inflammatory warfare in the body, and LDH values, which are indicative of cellular damage, with MPAD indicates that blood oxygenation, pulmonary vascular bed resistance and thus MPAD may be affected as the damage in the body increases (13-17). As in the study of Zhou et al., it has been shown in many studies so far that high LDH levels are associated with respiratory distress and ARDS (14,15).

The change of radiological findings of COVID-19 pneumonia according to the stage of the disease and time has been well described in previous literature studies (8). The most common pattern of virus-related pulmonary involvement is ground-glass opacities with periferobasal distribution. Although transformation into crazy-paving or consolidation pattern is an expected finding in the advanced stages of the disease, it may not occur in young patients and those with mild disease, and these ground-glass opacities may regress spontaneously. In other words, those with involvement in crazy-paving and consolidation pattern have more severe clinical symptoms and respiratory distress. Blood oxygenation is lower in these patients compared to patients with ground-glass infiltration, and oxygen support and even endotracheal intubation are required in most of them (7). The wider MPAD in this pattern and in patients with central or widespread involvement in our study indicates that MPAD is associated with respiratory distress. There are also recent literature studies supporting the results of our study. In the study of Esposito et al., it was shown that enlarged MPAD (≥ 31 mm) at admitting chest CT is an independent predictor of mortality in COVID-19 (18).Yildiz et al. showed that increased main pulmonary artery diameter is associated with poorer prognosis for patients with COVID-19 pneumonia in their study (19).

Our study has some limitations. The most important technical limitation of this retrospective study is the evaluation of a vascular structure on non-contrast examinations. However, achieving high quality of all exams in standard protocols with new generation devices greatly exceeds this limitation. Another limitation of the study is that the parenchymal imaging findings were performed by a single radiologist and the interobserver difference was not evaluated.

As a result; MPAD enlargement is associated with widespread infiltration in the pattern of crazy-paving or consolidation, CRP and LDH parameters, that proportional to the severity of the disease in COVID-19 pneumonia. Measuring MPAD during radiological evaluation will guide clinicians in terms of treatment plan and hospitalization.

DECLARATIONS

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Conflicts of interest

The author declares that there is no conflict of interest

Ethics approval

The study protocol was approved by local ethics committee (Date: 20.08.2020 No: 2020/18). The study complied with the Declaration of Helsinki.

Availability of data and material

The materials described in the manuscript will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Authors' contributions

Concept – D.E.T.Ş.; Design - D.E.T.Ş.; Supervision - D.E.T.Ş.; Resource - D.E.T.Ş.; Materials - D.E.T.Ş.; Data Collection and/or Processing - D.E.T.Ş.; Analysis and/or Interpretation - D.E.T.Ş.; Literature Search - D.E.T.Ş.; Writing - H.K.K., E.E.A.; Critical Reviews - D.E.T.Ş.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nutrition and Dietetics / Beslenme ve Diyetetik

Eating Behaviours of Lactating Women Differ by Infant Age and Maternal BMI

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ABSTRACT

Purpose: In lactation, women experience major changes in their lives as new internal and external demands for attention and care for themselves and the baby, also body mass index due to eating behaviours. Our aim was to define relationships between mindful eating and eating behaviours of breastfeeding mothers by baby's age and maternal BMI.

Methods: This cross-sectional study was conducted between October-November 2021 with 302 lactating mothers without chronic disease. Our study was approved by Ethics Committee of the Acibadem Mehmet Ali Aydinlar University. A questionnaire form that examined demographic data and Mindful Eating Questionnaire (MEQ-30) were applied. Anthropometric variables were reported by participants due to Covid-19 pandemic.

Results: Mean age of our participants was 30.6±4.2 years. Mothers with obesity had lowest score in MEQ-30 ($p<0.001$). Lactating mothers who were underweight had highest MEQ-30 score ($p<0.001$). It was shown that lactating mothers have highest MEQ-30 score in the first 6 months, and MEQ-30 scores decreased as baby grows ($p<0.001$).

Conclusion: Lactation period can be an appropriate time to bring about long-term changes in eating behavior. Healthcare professionals and teams can apply treatments focused on eating behavior and mindful eating for mothers with obesity in terms of their physical and emotional health, especially after the 6th month of breastfeeding.

Keywords: lactation, body mass index, mindful eating, eating, emotional eating.

Maternal BKİ Ve Bebeğin Yaşı Laktasyon Dönemindeki Kadınların Yeme Davranışlarını Değiştirebilir

ÖZET

Amaç: Emzirme döneminde kadınlar, kendilerine bakma ve bebeğe bakım verme sürecinde yeni içsel ve dışsal taleplerle baş ederken, ayrıca yeme davranışlarındaki değişiklikler nedeniyle beden kütle indeksi (BKİ) değerinde büyük değişiklikler yaşamaktadır. Bu araştırmadaki amaç, emziren annelerin beden kütle indeksi, yeme farkındalığı ve yeme davranışları arasındaki ilişkileri bebeğin yaşı ve maternal BKİ çerçevesinde değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel çalışma, Ekim-Kasım 2021 tarihleri arasında kronik hastalığı olmayan 302 emziren anne ile yapılmıştır. Çalışmamız Acıbadem Mehmet Ali Aydınlar Üniversitesi Etik Kurulu tarafından onaylanmış olup, katılımcılara demografik verileri inceleyen anket formu ve Yeme Farkındalığı Ölçeği (MEQ-30) uygulanmıştır. Covid-19 pandemisi nedeniyle antropometrik veriler katılımcılar tarafından rapor edilmiştir.

Bulgular: Katılımcılarımızın yaş ortalaması 30,6±4,2 yıl olarak saptanmıştır. Obezitesi olan anneler yeme farkındalığı ölçeğinden (MEQ-30) diğer gruplara göre daha düşük puan almıştır. ($p<0,001$). Zayıf anneler en yüksek MEQ-30 skoruna sahip olduğu belirlenmiştir ($p<0,001$). Emziren annelerin yeme farkındalığı düzeyinin ilk 6 ayda en yüksek olduğu, MEQ-30 puanlarının bebek büyüdükçe düştüğü gösterilmiştir ($p<0,001$).

Sonuç: Emzirme dönemi, yeme davranışında uzun vadeli değişiklikler meydana getirmek için uygun bir zaman dilimi olabilmektedir. Sağlık profesyonelleri ve ekipleri, özellikle emzirmenin 6. ayından sonra obezitesi olan annelere fiziksel ve duygusal sağlıkları açısından yeme davranışı ve farkındalığı odaklı tedaviler uygulayarak katkıda bulunabilir.

Anahtar Kelimeler: laktasyon, beden kütle indeksi, yeme davranışı, yeme, duygusal yeme.

Pregnancy is a strong predictor of long-term weight gain and obesity in women of childbearing age. Although adequate nutrition is important during pregnancy, excessive weight gain is not recommended, not just for physical (1) but also mental health (2). One of every two women with obesity cannot return to their pre-pregnancy weight after birth and encounter postpartum obesity. Gestational weight gain can be a risk of abdominal visceral fat increase and leads to the development of type 2 diabetes and cardiovascular disease later (2). Nutritional interventions aimed to reduce excessive body weight gain during pregnancy and postpartum obesity target changes in food intake as well as physical activity. Skouteris et al. (2010) emphasizes that psychological factors should have a more prominent role in intervention strategies in order to reduce effectively weight gain during pregnancy (3). Therefore, it is important to have an idea about underlying psychological mechanisms such as eating behaviors.

Eating behavior examines the mechanisms that direct the behavior in terms of how and under what conditions more people tend to eat (4). Studies clearly show that eating behaviors such as emotional, extrinsic, and restricted eating are associated with higher body mass index (BMI) and weight gain (5,6). Emotional changes during pregnancy, stronger perception of external stimuli and food cravings support the hypothesis that eating behaviors play an important role in weight gain during pregnancy. Emotional states and associated eating behavior can take on different intensities at various stages of pregnancy. This process, which is relatively stable during pregnancy, tends to increase during breastfeeding (7). In a meta-analysis examining the relationship between weight gain during pregnancy, postpartum obesity and eating behaviors, it showed that intuitive eating may be associated with decreased weight gain and reduced postpartum obesity during pregnancy. But there was no relationship between food cravings, external, emotional, disinhibited, uncontrolled and careful eating and postpartum obesity (4).

Despite the problems of unhealthy eating behavior, community-based public health approaches to treatment and prevention are not sufficient. There is a particular need for binge and emotional eating interventions, given their prevalence and physical, psychological and social consequences (8). The breastfeeding period is an appropriate moment to bring about long-term changes in women's eating behavior. Our hypothesis was lactating mother's mindful eating levels may change by the baby grows. Therefore, in our study it was aimed to define relationships between body mass index, mindful eating and eating behaviors of breastfeeding mothers by baby's age.

MATERIALS AND METHODS

This study was conducted in Medipol Mega Hospital between February and July 2020 with 302 breastfeeding mothers without chronic disease. Mean age of the mothers is 30.6 ± 4.2 years. The approval of the study was obtained from Ethics Committee of the Acibadem Mehmet Ali Aydinlar University with the number of 2021-19/25.

Data Collection

A questionnaire form that examined demographic data and Mindful Eating Questionnaire (MEQ-30) were applied to breastfeeding mothers. In the questionnaire form, mother's age, education level, anthropometric information, and baby's monthly age were included. Body weight and height information were reported by the participants. Body mass index was then calculated by researchers by taking the ratio of weight in kilograms to height in square meters.

Mindful Eating Questionnaire (MEQ-30)

MEQ-30 was used to measure the mindful eating status of breastfeeding mothers. With the scale originally named Mindful Eating Questionnaire (MEQ), which was developed by Framson et al. in 2009, associations between eating behavior, mindfulness, and emotional state can be questioned (9). Mindful Eating Questionnaire adapted into Turkish by Kose et al. (2017), includes seven sub-scales as disinhibition (mindless eating), emotional eating, eating control, mindfulness, eating discipline, conscious nutrition and interference (10). The higher the score on the scale, the higher the mindful eating level is detected. The sub-scales provide more detailed information about the sample's eating behaviors. In original form of MEQ Cronbach's alfa, was 0.640, Turkish form was 0.733, in this study it was found as 0.781.

Data were analyzed with IBM SPSS Statistics 22.0. In comparisons between groups, the Kruskal-Wallis test was used because the data did not show normal distribution. Chi-square test was used to compare two categorical groups. Significance was evaluated at the $p<0.05$ level. Height and body weight were measured, and Body Mass Index (BMI) was calculated using the formula: body weight (kg) / height^2 (m^2). The underweight group was excluded from the chi-square test due to the fact that the distribution between the groups was not found to be statistically suitable (expected value = 12.5%) while classifying the BMI.

RESULTS

The evaluation of the data obtained from this study was shared below. Mean age of breastfeeding mothers participating in the study was 30.6 ± 4.2 years (min. 20, max. 44), and their mean BMI was 24.5 ± 4.5 kg / m^2 (min. 15.1 kg / m^2, max. 41.3 kg / m^2). When the BMI values of the participants were considered according to the classification of the World Health Organization (11), it was mostly (53.3%) within normal BMI ranges.

Mother's mindful eating levels according to the BMI and their baby's age was shown in Table 1. Mothers with obesity had lowest scores in MEQ-30 (p<0.001) (Table 1). While the mothers with underweight BMI had the highest mindful eating score (p<0.001), it was found that the mindful eating levels of the mothers was higher in the first 6 months of lactation (p<0.05).

Participant's mindful eating and sub-scale scores according to BMI and baby's age were evaluated (Table 2). According to the BMI classification, mothers with underweight BMI had higher scores on the MEQ-30 and subscales compared to the other BMI groups, but only conscious nutrition was statistically significant (p<0.001). When the mother's mindful eating levels were evaluated according to the age of the baby, it was seen that they have the highest MEQ-30 score in the first 6 months, and the mindful eating score decreases as the baby grows (p<0.001). When the sub-scales were evaluated; disinhibition, eating control (p<0.001), conscious nutrition and interference (p<0.05) were high in mothers whose babies were 0-6 months old; emotional eating sub-scale was found to be higher in those with babies over 24 months (p<0.001).

Table 1. Mother's mindful eating level according to BMI and baby's age

	MEQ-30 Scores			
	MEQ-30 ≥ 3	**MEQ-30 <3**	***X²***	***p***
BMI				
Underweight	3.74±0.26(n=18)	- (n=0)	14.708	0.001**
Normal	3.58±0.35 (n=143)	2.67±0.19 (n=18)		
Overweight	3.47±0.32 (n=67)	2.66±0.23 (n=24)		
Obese	3.34±0.31 (n=21)	2.53±0.22 (n=11)		
Baby's age (monthly)				
0-6	3.57±0.35 (n=130)	2.57±0.25 (n=18)	7.303	0.026*
6-12	3.51±0.33 (n=67)	2.69±0.16 (n=16)		
≥12	3.51±0.54 (n=52)	2.64±0.23 (n=19)		

BMI: Body Mass Index, MEQ-30: Mindful Eating Questionnaire. *p<0.05, **p<0.01.

Table 2. MEQ-30 scores and sub-scales according to BMI and baby's age

		BMI Classification of Mothers						**Baby's age (monthly)**					
	Total (n=302)	**Under-weight (n=18)**	**Normal (n=161)**	**Pre obese (n=91)**	**Obese (n=32)**	***X²***	***p***	**0-6 (n=148)**	**6-12 (n=83)**	**12-24 (n=64)**	**> 24 (n=7)**	***X²***	***p***
MEQ-30	3.4±0.5	3.74±0.26	3.47±0.44	3.25±0.46	3.06±0.48	7.383	0.061	3.45±0.47	3.35±0.44	3.29±0.49	3.14±0.59	38.280	0.000**
DI	3.3±0.7	3.93±0.55	3.41±0.74	3.15±0.73	2.98±0.85	7.200	0.066	3.43±0.73	3.24±0.77	3.19±0.76	2.80±1.25	23.851	0.000**
EE	3.4±1.1	4.07±0.61	3.56±0.99	3.13±1.03	2.64±1.04	2.279	0.517	3.45±1.01	3.30±1.11	3.24±1.01	3.48±1.35	32.759	0.000**
EC	3.8±0.9	4.45±0.67	4.02±0.89	3.46±0.97	3.44±0.74	5.785	0.123	3.90±0.92	3.80±0.92	3.70±0.99	3.13±1.04	37.268	0.000**
MN	3.3±0.4	3.24±0.48	3.20±0.36	3.29±0.41	3.26±0.48	1.540	0.673	3.25±0.43	3.26±0.40	3.19±0.31	3.22±0.29	2.889	0.409
ED	3.3±0.7	3.44±0.44	3.21±0.36	3.27±0.71	3.03±0.82	6.245	0.100	3.23±0.78	3.43±0.69	3.44±0.64	3.04±0.73	7.131	0.068
CN	3.3±0.5	3.45±0.48	3.32±0.52	3.25±0.55	3.07±0.48	22.148	0.000**	3.43±0.53	3.19±0.47	3.07±0.53	3.20±0.46	8.922	0.030*
IN	3.6±0.8	3.75±0.72	3.71±0.76	3.45±0.79	3.22±0.96	4.079	0.253	3.67±0.81	3.51±0.78	3.47±0.83	3.35±0.69	12.137	0.007*

BMI: Body Mass Index, MEQ-30: Mindful Eating Questionnaire, DI: Disinhibition, EE: Emotional Eating, EC: Eating Control, MN: Mindfulness, ED: Eating Discipline, CN: Conscious Nutrition, IN: Interference. *p<0.05, **p<0.001.

Table 3. Correlation of mother's age and BMI, baby's age with MEQ-30 and its sub-scales (n=302)

	BMI		Mother's age		Baby's age	
	r	*p*	*r*	*p*	*r*	*p*
BMI	-	-	0.136	0.018*	-0.196	0.001**
MEQ-30	-0.333	0.000**	0.072	0.214	-0.172	0.003**
DI	-0.253	0.000**	0.098	0.091	-0.169	0.003**
EE	-0.312	0.000**	0.078	0.177	-0.092	0.110
EC	-0.366	0.000**	-0.127	0.027*	-0.133	0.021*
MN	0.070	0.225	0.011	0.856	-0.059	0.303
ED	-0.126	0.028*	0.247	0.000**	0.098	0.088
CN	-0.116	0.044*	0.040	0.490	-0.279	0.000**
IN	-0.197	0.001**	0.023	0.689	-0.115	0.046*

BMI: Body Mass Index, MEQ-30: Mindful Eating Questionnaire, DI: Disinhibition, EE: Emotional Eating, EC: Eating Control, MN: Mindfulness, ED: Eating Discipline, CN: Conscious Nutrition, IN: Interference. *p<0.05, **p<0.01.

There were some correlations between BMI and age of mother, baby's age, and MEQ-30, sub-scale scores. As the baby's age increased, the mother's BMI decreased (r=-0.196, p=0.001) (Table 3). The age of the baby and the mother's MEQ-30 (r=-0.172, p=0.003) score, and perspective from sub-scales; disinhibition (r=-0.169, p=0.003), eating control (r=0.133, p=0.021), conscious nutrition (r=-0.279, p=0.000) and interference (r=-0.115, p=0.046) factors were negatively correlated, but there were no correlations with emotional eating and eating discipline. As the mother's age increased, the BMI (r=0.136, p=0.018) increases. When mindful eating and sub-scale scores were evaluated, mother's age was correlated negatively correlated with eating control (p=0.027) and positively with eating discipline (p=0.000). As mother's BMI increased, MEQ-30, disinhibition, emotional eating, eating control and interference factors decrease statistically significantly (p=0.000). In addition, it was found to be negatively related to eating discipline and conscious nutrition (p<0.05).

DISCUSSION

Lactating mothers' attitudes towards disinhibition, conscious nutrition, emotional and mindful eating subject to change by breastfeeding. Our hypothesis was accepted as mothers' mindful eating levels and eating behaviors changed, especially in the first 6 months of infants and after 2 years of age during breastfeeding.

In an intervention study with lactating women, obese lactating women had higher mindful eating scores (2). Weight management in lactation may positively affect food choices on healthy eating (7). In our study, mothers with obesity had lowest mindful eating scores and mothers were more mindful in eating for the first 6 months of the baby. And mindful eating scores were decreased as the babies were growing. Mothers who have 1-3-year-old children had greater nutritional knowledge and lost more weight (12). Mothers whose babies were 0-6 months old had more eating control and conscious in nutrition, also they were not affected negatively by interference. It seems to be that for the first months of baby, mothers were paying more attention and more mindful about eating.

Mothers that lactating between 3-15 months, described breastfeeding as 'satisfactory' (13), having a relationship with baby can prevent emotional eating (14). Emotional eating can predict postpartum weight retention (2). Positive emotional and social changes during lactation provides healthy eating choices and behaviors (15). Emotional eating may be prevented by intuitive eating in the first year of lactation (16). In this study, emotional eating, mindfulness, conscious nutrition sub-scales, which decreased in the first year after birth, increased again after first year of lactation. Meanwhile, mindful eating scores continue to decrease. And also, mothers who had underweight and normal BMI more conscious in nutrition than overweight and obese ones. Adequate and balanced nutrition is important in the postpartum period as in every period of life. Conscious nutrition is at the forefront for adequate and balanced nutrition. Mindful eating and intuitive eating are similar in approach to postpartum eating behaviors (4) that is why studies with intuitive eating has been used in comparisons. But mothers with babies over 24 months could cope with more emotional eating. Prospective and interventional studies showed that disinhibition had no relations with postpartum weight loss

(2,16-17). On the contrary, we found that postpartum body weight had a negative correlation with disinhibition. And also, our participants' BMI increase was related to emotional eating, eating control and discipline, conscious nutrition, interference decrease that showed as high mindful eating scores. Body weight management in lactation can prevent emotional eating and lead to conscious and mindful eating.

Pregnancy has an effect on craving high fat food and as a consequence weight gain (18). In a study with lactating women, their eating behaviors was not affected by distraction (2). In a systematic review that lactation and postpartum weight changes were unclear (13). In a meta-analysis, significant associations found between body weight and eating behavior during pregnancy and the postpartum period (19), but a different meta-analysis showed that there were no relations between eating behaviors and postpartum weight (4). In the present study, when babies were growing, mothers' BMI were decreasing, but their mindful eating levels were on the wane, too. Mothers that had older babies had little control and conscious on eating or nutrition. And also, mothers' BMI can have a bidirectional effect on eating behaviors. Quansah et al. (2019) reported that intuitive eater mothers had lower postpartum weight (16). And in our study as expected, increased BMI had a negative effect on mindful eating. Understanding the reasons which eating behaviors change postpartum weight (gain or retention) can be helpful for a preventative or therapeutic approach (4). While there were statistically significant differences in sub-scales between the groups in the evaluation of the data of the participants, we couldn't find similar results in the correlation analyses. This may be because our research was not intervention research.

There are so many studies on pregnancy and eating behaviors (18). As far as we know, it was the first study about mindful eating in lactating mothers. Our study had some limitations as lack of information about body weight and mindful eating levels prior to pregnancy. Future studies can be made with previous information or have study in a prospective nature.

CONCLUSION

Lactation period can bring long-term changes in body weight and eating behaviors. In pre-pregnancy, during pregnancy and lactation periods, women should be educated about nutrition so they can be more conscious. In order for their physical and emotional health, especially after the 6th month of breastfeeding, healthcare team should recommend provide more trainings about weight management and eating behaviors that may change.

DECLARATIONS

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Conflicts of Interest

No potential conflict of interest was reported by the authors.

Ethics Approval

The protocol of the study was approved by the Ethical Committee of the Acibadem Mehmet Ali Aydinlar University with the number of 2021-19/25.

Availability of Data and Material

All authors accept that data and material is available.

Authors' Contribution

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

Determining the Knowledge and Attitudes of Nurses about Catheter Associated Urinary Tract Infections

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ABSTRACT

Aim: The aim of this study is to evaluate the knowledge and attitudes of nurses about the urinary catheter associated urinary tract infections.

Material method: This research is a descriptive study. The study was conducted between April and May 2021 in a medical faculty hospital. The sample of the study consisted of 220 nurses working in the medical faculty hospital. The data were collected online through an introductory information form and "Catheter Associated Urinary Tract Infections Control Precautions Scale" (CAUTICPS).

Findings: The CAUTICPS mean score of nurses was 64.01 ± 8.09 and their knowledge and attitudes were high. It was determined that the difference between the variables of receiving education about infections associated with urinary catheter, knowing about the surveillance rate of the institution and the employed unit and the total mean score of CAUTICPS was statistically significant ($p<0.05$). It was determined that the knowledge levels of the nurses who received training, knew about the surveillance speed and were employed in the intensive care unit were higher. While there was a positive, weak significant correlation was found between the age and mean scores of CAUTICPS ($p<0.05$), there was no significant correlation between the duration of employment and total scale score ($p>0.05$).

Conclusion and recommendations: It was determined that the knowledge levels of the nurses about preventing the catheter associated urinary tract infections were high. It is recommended to provide nurses having insufficient knowledge with in-service training. In addition, nurses should play an active role in taking the infection control measures concerning the healthcare of institutions and their surveillance follow-up.

Keywords: Urinary Tract Infections, Urinary Catheterization, CAUTI, Nursing care

Hemşirelerin Kateter İlişkili Üriner Sistem Enfeksiyonlarına Yönelik Bilgi ve Tutumlarının Belirlenmesi

ÖZET

Amaç: Bu araştırma hemşirelerin üriner kateter ilişkili üriner sistem enfeksiyonlarına yönelik bilgi ve tutumlarının değerlendirilmesi amacıyla yapılmıştır.

Materyal metod: Araştırma tanımlayıcı türdedir. Araştırma bir tıp fakültesi hastanesinde Nisan –Mayıs 2021 tarihleri arasında yürütülmüştür. Araştırmanın örneklemini tıp fakültesi hastanesinde görev yapan 220 hemşire oluşturmuştur. Veriler tanıtıcı bilgi formu ve "Kateter İlişkili Üriner Sistem Enfeksiyonları Kontrol Önlemleri Ölçeği (KİÜSEKÖÖ)" ile online olarak toplanmıştır.

Bulgular: Hemşirelerin KİÜSEKÖÖ' den aldıkları ortalama puan 64.01 ± 8.09 olup bilgi ve tutumları yüksektir. Üriner kateter ilişkili enfeksiyonlar hakkında eğitim alma durumu, kurumun sürveyans hızını bilme ve çalışılan birim değişkenleri ile KİÜSEKÖÖ toplam puan ortalaması arasındaki farkın istatistiksel açıdan anlamlı olduğu belirlendi ($p<0.05$). Eğitim alan, sürveyans hızını bilen ve yoğun bakımlarda görev yapan hemşirelerin bilgi seviyelerinin daha yüksek olduğu belirlendi. Yaş ile KİÜSEKÖÖ puan ortalaması arasında pozitif yönde, zayıf düzeyde anlamlı ilişki olduğu belirlenirken ($p<0.05$), görev süresi ile ölçek toplam puanı arasında anlamlı bir ilişki olmadığı belirlendi ($p>0.05$).

Sonuç ve öneriler: Hemşirelerin kateter ilişkili üriner sistem enfeksiyonlarının önlenmesine yönelik bilgi seviyelerinin yüksek olduğu belirlendi. Bilgi yetersizliği olan hemşirelere hizmet içi eğitimlerin verilmesi önerilir. Ayrıca, kurumlarda sağlık bakımı ile ilişkili enfeksiyon kontrol önlemlerinin alınmasında ve surveyans takiplerinde hemşireler aktif rol almalıdır.

Anahtar Kelimeler: Üriner Sistem Enfeksiyonları, Üriner Kateterizasyon, CAUTI, Hemşirelik bakımı

Healthcare-associated infections are the infections that can progress with morbidity and mortality that occur at least 48 hours after admission or within 30 days after discharge, not in incubation period at the patient's admission to the hospital and increase the duration and cost of hospitalization (1,2). Catheter associated urinary tract infections (CAUTI) are among the healthcare-associated infections. CAUTI defined as the findings of urinary tract infections and significant bacteriuria development among patients who had urinary catheters or whose catheters were removed within the last 48 hours (3,4). According to the 2019 national surveillance data of Turkey, the rate of CAUTI varies between 0.2 and 1.8 in the intensive care units CAUTI amount / UC days *1000) (5). The urinary tract infections are 23% of the infections in the intensive care units and 95% of these infections are CAUTI (6). Like other healthcare related infections, CAUTIs cause the prolongation of hospital stay, excessive medication, poor patient comfort, increased health costs and loss of nursing labor. (7)

Many factors are effective in the prevention of CAUTI. Complying with the protocols developed concerning urinary catheter care, providing healthcare staff training, making CAUTI surveillance follow-up, removing the urinary catheter when the indications cease and not applying catheterization without indications are the measures to be taken for preventing CAUTI (8,9,10). If there is an indication, it is under the nurses' responsibility upon the doctor request to insert the urinary catheter, provide catheter care, change the drainage bag and make the follow-up (11). For this reason, the effects of nurses' knowledge, attitude and compliance with the infection control measures are major in the prevention of CAUTI.

The studies have reported that nurses do not have sufficient knowledge about the prevention of CAUTI (12, 13). Based on the study by Karadağ Arlı, it was revealed that nurses had a high level of knowledge (14). The fact that nurses have high level of knowledge and attitude about CAUTI will lead to a decrease in CAUTI rates, the prevention of infection related mortality and morbidity, an increase in patient satisfaction, and a decrease in hospital expenses. This study was conducted for the purpose of evaluating the knowledge and attitudes of nurses about the prevention of CAUTIs.

METHODS

Design: The research was a descriptive study.

Place and date of the study: The research was carried out between April and May 2021 in a medical faculty hospital.

Population: The study was conducted in a medical faculty hospital where the urinary catheterization intervention and follow-up frequently takes places. The population of the study consisted of 900 nurses working in the medical faculty hospital.

Sample: Sample of the study consisted of 220 nurses. The sample size was calculated by using the data of a study in which the knowledge and attitudes of nurses working in the intensive care unit about urinary catheterization were evaluated (15). It was determined that the sample should be 194 nurses, with an alpha margin of error of 0.05, a 95% confidence interval and an effect size of 0.237. In this study, using the data obtained from the calculation made according to the attitude score averages, the sample size was determined as 194 nurses, increased by 15% compared to the literature and completed with 220 nurses (16). The inclusion criteria were determined as follows; working as a nurse in the medical faculty and to be aged between 18 and 60 years. Nurses who are working in the hospital staff but were not actively working because of being on leave or sick leave were not included in the scope of the study.

Data Collection Tools

Introductory Information Form: It is the form which was prepared by the researcher and includes the socio-demographic characteristics of the participants such as age, gender, and educational background.

Catheter Associated Urinary Tract Infections Control Precautions Scale(CAUTICPS): This scale was developed by Karadağ Arlı and Bakan (17). The scale is a 5-point Likert type and consists of 15 items. While calculating the scale score, the 13th item is scored reversely. High score signifies good knowledge and attitude level. The lowest score to be obtained from the scale is 15, whereas the highest score is 75. The Cronbach's Alpha value of the scale is 0.83. Permission was received from the author through email. The Cronbach's Alpha value of the scale is 0.91 in the present study.

Data Collection Method: The online questionnaires were transmitted to nurses through hospital management quality department by email or other social media applications. The first section of the questionnaire includes the statement "I would like to participate in the study" as well

as participation conditions and purpose and the name of the researchers in order to get the written consent of the participants. The nurses giving the approval in this section participated in the study. Nurses agreeing to participate in the study gave their responses to the introductory information form and Catheter Associated Urinary Tract Infections Control Precautions Scale. The received responses were checked through the system and recorded.

Data Analysis: Number, percentage, mean score, and standard deviation were used to analyze the data. In the comparing knowledge scores with characteristics of nurses, Mann-Whitney-U test was used for non-normally distributed data in comparison of two groups. Kruskal Wallis test was used for non-normally distributed data in comparison of more than two groups. In groups creating significance, Post-hoc tamhane parametric test was used in order to determine which group caused the difference. Spearman's correlation analysis was made in the comparison of several variables and scale total score. The significance level was accepted as $p<0.05$ and in the confidence interval of 95%.

Ethics: Ethics committee approval from Health Sciences Scientific Research Ethics Board of a university (03.02.2021/16) and written permission from the medical faculty hospital were obtained before starting to conduct the study. Permission to use the Catheter Associated Urinary Tract Infections Control Precautions Scale was obtained from the authors.

Limitations of the Research: The limitation of the study is that the study was conducted in a hospital. The results will be related to the nurses working only in the concerning hospital. They cannot be generalized.

RESULTS

Table 1. Total Mean Scores of the Catheter Associated Urinary Tract Infections Control Precautions Scale of the nurses

Scale total score	64.01 ± 8.09 (Min: 17 Max: 74)

Total mean scores of the CAUTICPS scale of the nurses is 64.01 ± 8.09 (Min: 17 Max: 74).

Table 2. Total Mean Scores of the Catheter Associated Urinary Tract Infections Control Precautions Scale based on the demographic and professional characteristics of the Nurses

		N	%	M±SD	Test Value and Significance
Gender	Female	182	82.7	64.19 ± 8.58	U= 2721 p= 0.380
	Male	38	17.3	63.15 ± 5.14	
Educational Background	High School	39	17.7	61.64 ± 9.69	KW=7.40 p =0.060
	Associate degree	35	15.9	64.57 ± 4.56	
	Bachelor's degree	123	55.9	64.34 ± 7.62	
	Graduate	23	10.5	65.43 ±11.04	
Clinic	Intensive Care [a]	46	20.9	68.15± 3.85	KW= 42.59 **p= 0.000** **a>c, d, g**
	Internal Medicine Clinics [b]	47	21.4	65.25± 8.62	
	Surgical Clinics [c]	38	17.3	60.81 ±11.51	
	Emergency [d]	43	19.5	60.65 ±7.67	
	Operating Room [e]	22	10.0	64.90 ± 5.17	
	Pediatrics [f]	8	3.6	66.87 ± 5.69	
	Other [g]	16	7.3	62.50 ± 3.94	
Status of receiving education on prevention of CAUTIs	Yes	78	35.5	65.88 ± 9.21	U= 3615 **p= 0.000**
	No	142	64.5	62.99 ± 7.24	
Status of knowing the CAUTI surveillance rate of the institution	Yes	86	39.1	65.72 ± 7.51	U= 4247 **p= 0.001**
	No	134	60.9	62.92 ± 8.28	
Status of having a CAUTI related protocol	Available	138	62.7	64.39 ± 8.73	U= 4863 p=0.081
	N/A	82	37.3	63.37 ± 6.89	
Average age (years)	33.03 ± 9.55 (Min :20 Max 59)				
Employment (years)	12.00 ± 10.13 (Min:1 Max:40)				

Abbreviations: CAUTI: Catheter associated urinary tract infections, M, mean, SD: Standart Deviation, U:Mann whitney U, KW: Kruskall Wallis, p: 0.05 significance level

According to Table 2; 82.7% of the nurses participating in the research are female, 55.9% have a bachelor's degree, 35.5% have received training on CAUTI prevention, 60.9% of the nurses didn't know the CAUTI surveillance rate of their institution. The average age of the nurses was 33.03 ± 9.55. Mean employment duration was 12.00 ± 10.13 years.

There was a significant difference between nurses status of receiving education on prevention of CAUTIs, in terms of CAUTICPS total scores ($p < 0.05$). The CAUTICPS total scores of nurses knowing the surveillance rate of their institution were significantly high ($p < 0.05$). The CAUTICPS scores of the nurses were significant according to the clinics they worked in ($p= 0.000$). The results of Tamhane post-hoc analysis revealed that there was a significant difference between the nurses working in intensive care unit and those working in surgical ($p=0.011$), emergency ($p=0.000$) and other clinics ($p=0.001$) in terms of CAUTICPS total scores. Nurses working in the intensive care unit had significantly high scale scores.

Table 3. Correlation between the total mean score of the Catheter Associated Urinary Tract Infections Control Precautions Scale and the Age and Total Duration of Employment

	Total Mean Score of the Catheter Associated Urinary Tract Infections Control Precautions Scale	
	r	p
Age	0.171	0.012
Duration of employment	0.115	0.090

r: Spearman Correlation coefficient; p: 0.05 significance level

There was a positive correlation between CAUTICPS total mean score and age. There was no correlation between the duration of employment and CAUTICPS total scores of the participants.

DISCUSSION

This study was conducted for the purpose of assessing the knowledge and attitudes of nurses about prevention of CAUTI. It is reported that urinary catheter is inserted to patients treated with CDC admission at the rate of 15-25%. Although urinary catheterization is required for many patients, the justifications related to the indications are not explained for approximately 50% of the patients (18). More than 60% of hospital-acquired urinary tract infections are associated with urinary catheter (19). CAUTI can be decreased at the rate of 65-70% through evidence based standard measures of healthcare professionals (20). Among the healthcare professionals, nurses in charge of implementing, care and follow-up of the urinary catheterization practice can be a significant transformation agent in decreasing the CAUTI rates (21).

The CAUTICPS total mean score of the nurses participating in the present study was 64.01+ 8.09. The knowledge and attitude levels of the nurses on catheter associated urinary tract infections were high. Likewise, Arlı Karadağ 2020 et al., also found that the knowledge levels and attitudes of the nurses were high (14). However, many studies have reported that the knowledge levels of nurses about CAUTI were not at the desired level (13,22,23). Trainings on CAUTI and its prevention should be arranged for nurses within the scope of continuous in-service training programs. The most effective method in the prevention of CAUTI is to decrease the use of catheter and to remove the catheter as earliest as possible (24). It is important for nurses to have up-to-date knowledge in the prevention of CAUTIs and they maintain an effective patient care by using this knowledge in practice (25).

The results of the present study revealed that there was a significant difference between the CAUTICPS total mean score of intensive care nurses and those working in surgical, emergency, and other clinics. Nurses working in the intensive care had significantly high CAUTICPS total mean scores. Intensive care units are risky areas for CAUTI since urinary catheter is applied to more patients in intensive care units, catheter is inserted for a long time, and resistant microorganisms are mostly isolated. In this sense, intensive care unit nurses have important responsibilities. Urinary tract infections constitute 23% of the infections in the intensive care unit and it is reported that approximately 95% of the urinary tract infections in the intensive care units are associated with catheter (6)

The results of the present study indicated that the knowledge and attitudes of nurses receiving education on CAUTI were significantly higher than those who did not. It was reported that the knowledge and attitudes of the nurses trained on infection control measures were high (14) and following the education, the CAUTI rates declined significantly (26). The training, attitudes, and inspections of nurses are important as required by the role of being a primary caregiver in the prevention of CAUTI. The principle suggestions for CAUTI prevention include inserting the catheter only when there is an indication and assessing its necessity, using it for a necessary duration, inserting it by trained persons through complying

with aseptic techniques, lack of interruption of urine flow, implementation of hand hygiene and the application of standard measures. In addition to these suggestions, training the healthcare professionals about catheter care and removing the catheter as earliest as possible are among the common suggestions by the guidelines published by professional organizations (8, 25,27).

Results of the present study indicated that there was a significant difference between knowledge and attitudes of the nurses knowing the surveillance rate of their institution and those who did not. In Turkey, the healthcare associated infection rates are reported through the data coming from the hospitals via national healthcare services related infection surveillance system. The CAUTI rate of each hospital is stated in this report. The required regulatory activities are planned and implemented based on these infection rates and healthcare related infection rates are tried to be decreased.

According to results of the present study, as age of the participants increased, their knowledge and attitudes about the prevention of CAUTIs increased. In the study carried out by Aylaz et al., (2015) for determining the knowledge levels of nurses on hospital infections, they found that older nurses had higher knowledge scores than those who were younger (28). It is considered that with increasing age nurses have an increase in their knowledge and attitudes as a result of the increase in their professional knowledge, skills and experiences. According to results of the present study, there was no significant correlation between the duration of employment and the scale total scores. The average duration of employment of the nurses participating in the present study was 12.00±10.13 years. In contrast to the present study, there are studies indicating that as the nurses' duration of working in the profession increased, their level of knowledge on healthcare related infections increased (29).

CONCLUSION

Nurses are healthcare team members having the most frequent communication with individual patients in charge of interventions such as applying the urinary catheter on the individual, its follow-up and drainage, which is why they have significant roles in decreasing CAUTIs. According to results of the present study, the knowledge and attitudes of nurses about CAUTIs were high. The knowledge and attitudes of intensive care nurses about CAUTIs were significantly high. The knowledge and attitudes increase with the increasing age. The scale scores of the nurses receiving education on CAUTIs and knowing the CAUTI surveillance rate of their institution were significantly high. Based on these results, it is recommended that;

- The nurses be provided with continuous in-service training about prevention of CAUTIs in line with the up-to-date guidelines
- Nurses should conduct scientific studies on CAUTIs
- Studies be planned with more participants and with other health professions.

DECLARATIONS

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Conflict of interests: The authors declare that there is no personal or financial conflict of interest within the scope of the study.

Ethical Approval: Health Sciences Scientific Research Ethics Board of a university (03.02.2021/16)

Author Contribution: Research idea: HTP, HA, Research design and data collection: HTP, HA, analysis and writing article: HTP, HA.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

Professional Self-Concept and Critical Thinking of Pediatric Nurses in Turkey

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ABSTRACT

Objectives: There has been an increasing demand for nurses with advanced professional qualifications. A professional self-concept and critical thinking in nurses are necessary for determining complicated patient care needs and for finding and applying accurate and practical solutions in patient management. This study conducted to determine level of critical thinking and professional self-concept and the relationship between these concepts in pediatric nurses.

Study Design: The study was conducted with 120 nurses working at a public hospital in Middle Anatolia in Turkey. The data were collected using a questionnaire, the Professional Self-Concept Scale in Nurses (PSCSN) and the California Critical Thinking Disposition Inventory (CCTDI).

Results: A significant positive association was found between the mean PSCSN and CCTDI scores of the nurses ($p<0.05$). Educational and employment status, voluntary choice of job and communication with other health care professionals influenced the mean scores of professional self-concept and critical thinking in nurses.

Conclusion: It was determined that critical thinking ability is important in developing professional self-concept, and educational status, working position, choosing the profession willingly and communication with the other healthcare staff were effective on professional self-concept and critical thinking.

Keywords: Critical thinking, Pediatric nurses, Professional self-concept

Pediatri Hemşirelerinde Profesyonel Benlik Kavramı ve Eleştirel Düşünme

ÖZET

Amaç: Son yıllarda profesyonel nitelikleri gelişmiş hemşirelere duyulan gereksinim giderek artmaktadır. Hemşirelerin karmaşık hasta bakım gereksinimlerini saptayabilmeleri, en doğru ve pratik çözümü bulup hızla uygulamaları ve profesyonel bakım sunabilmeleri için profesyonel benlik kavramı ve eleştirel düşünmeleri gerekmektedir. Bu çalışma, çocuk hemşirelerinde eleştirel düşünme düzeyi ile mesleki benlik kavramı ve bu kavramlar arasındaki ilişkiyi belirlemek amacıyla yapılmıştır.

Çalışma Planı: Çalışma Türkiye'de Orta Anadolu'da bir devlet hastanesinde çalışan 120 hemşire ile gerçekleştirildi. Veriler Tanıtıcı Bilgi Formu, Hemşirelerde Profesyonel Benlik Kavramı Ölçeği (HPBKÖ) ve California Eleştirel Düşünme Eğilimi Envanteri (CEDEE) kullanılarak toplandı.

Bulgular: Hemşirelerde Profesyonel Benlik Kavramı Ölçeği (HPBKÖ) ile California Eleştirel Düşünme Eğilimi Envanteri (CEDEE) puan ortalamaları arasında pozitif yönde anlamlı bir ilişki bulunmuştur ($p<0.05$). Hemşirelerde eğitim ve istihdam durumu, mesleği isteyerek seçme ve diğer sağlık profesyonelleriyle iletişim, mesleki benlik kavramı ve eleştirel düşünme ortalamalarını etkilediği tespit edilmiştir.

Sonuç: Mesleki benlik kavramının geliştirilmesinde eleştirel düşünme yeteneğinin önemli olduğu, mesleki benlik kavramı ve eleştirel düşünme üzerinde eğitim durumu, çalışma pozisyonu, mesleği isteyerek seçme ve diğer sağlık personeli ile iletişimin etkili olduğu belirlenmiştir.

Anahtar Sözcükler: Eleştirel düşünme, Pediatri hemşireleri, Profesyonel benlik kavramı

There have been increasing demands and expectations for nurses with advanced professional qualifications who have high motivation and who are receptive to changes within the healthcare system because of more complicated and various patient groups, more complex and new treatment methods and recent rapid developments in science and technology (1). These scientific and technological advances lead to nurses living a proceeding of adaptation from a traditional model to professionalism and increase the importance and expectations of nurses to provide quality nursing care (1,2). Despite these increased requirements and expectations for nurses, there are reported to be problems regarding the professional qualifications of nurses due to recent concerns about the social image of the nursing profession and the problems caused by the lack of nurses (3,4).

A professional attitude or "professionalism" is a frame used by professionals in defining their works as a community role; thus, professionals emphasize value commitments based primarily on the "professional status" of their work (5). Nursing, which is currently becoming a recognized profession, aims at protecting and promoting the health of individuals and the community at large, thus preventing diseases and increasing the coping capacity of individuals and social groups using care and rehabilitative services (6). Professional identification means to be the nurses' perception of the profession and their adoption of moving in the role of a nurse. A nurse's Professional identity represents the nursing philosophy and the values and notions that guides the attitudes and allinteractions of the nurse (5,6). Nurses should improve their thinking and analytical powers to find solutions to contemporary problems, to determine the needs for complicated patient care, to quickly apply the most accurate and practical solutions and to provide professional care (6,7). Especially special field nurses such as pediatric nursing need to easily adapt to innovations and developments, search for knowledge, ask questions, think critically, find solutions to problems and have social awareness by maintaining intellectual development (6,8). Because pediatric nurses should have well-developed critical thinking skills and a professional self-concept to communicate and interact with children and to coordinate care according to the age and period characteristics of the children. Critical thinking and professional self-concept have gained enhanced importance. For the reasons explained above, this study was conducted to examine both professional self-concept and critical thinking, which are very important in the development of professional awareness and professional identity in pediatric nursing.

MATERIALS and METHODS

This descriptive study carried out for defining level of critical thinking and professional self-concept and the relationship between these concepts in pediatric nurses.

This study was conducted in pediatric clinics of a public hospital. At the time of this study, 150 nurses worked in pediatric clinics of a public hospital, 120 of these nurses participated in the study. We explained the aim of this study to the pediatric nurses participating in this study. The questionnaires and return envelopes were delivered directly to pediatric nurses. Survey and question forms in the return envelopes were given directly to pediatric nurses (return rate 80%). After the forms were filled, they were handed over to the research team in sealed envelopes.

The data were collected by question form that included the socio-demographic characteristics of the participants, the Professional Self-Concept Scale in Nurses (PSCSN) and the California Critical Thinking Disposition Inventory (CCTDI).

The Professional Self-Concept Scale (PSCSN)

The Professional Self-Concept Scale (PSCSN) in Nurses is a 36-item scale with 3 subscales (occupational satisfaction, professional competence, and professional attitude and skills) using a 4-point likert-type scale. The PSCSN was created for measuring the level of professional self-concept and validity; the reliability research was conducted by Sabancıoğulları, Doğan, and Bircan. The Cronbach's alpha was 0.87, and the test/re-test reliability was 0.76. The scale has 8 negative and 28 positive statements; the positive statements are scored ranging from "1=totally disagree" to "4=completely agree," whereas the negative statements are scored inversely. A higher score shows that nurses have positively improved their professional self-concept (9).

The California Critical Thinking Disposition Inventory (CCTDS)

The California Critical Thinking Disposition Inventory (CCTDS) was created for measuring the level of critical thinking by Facione in 1990 (10). The scale consists of 75 questions prepared as a 6-point Likert-type scale ranging from "6=totally agree" to "1=totally disagree". A score of over 50 for each factor indicates advanced critical thinking, while a score below 40 indicates poor critical thinking. The scale consists of 6 sub-sizes (truth-seeking, open-mindedness, analyticity, systematicity, self-confidence and inquisitiveness). While 280 and below from the scale total point

shows the level of weak critical thinking, more than 350 points indicate the advanced critical thinking level. The Cronbach's alpha for the CCTDS was 0.92. The Cronbach's alpha of each factor ranged from 0.71 to 0.80 (11, 12). The Turkish version of the scale consists of 6 factors and 51 items. The validity and reliability study of the scale was studied by Kökdemir in 2003. As a result of the analysis, it was determined that the Cronbach alpha value of the whole scale was 0.88 and the Cronbach alpha value of each factor was between 0.61 and 0.78 (11).

Ethical consideration

Before the initiation of this study, ethics committee (2013/55) and the institutional permission was obtained. In addition, the aim of this study was explained to the pediatric nurses participating in this study.

Statistical Analysis

IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA) package program was used to assess the data of the study. Distribution characteristics of the databy Kolmogorov-Smirnov normality test. Mann-Whitney U test was used in the comparison of two independent groups. ANOVA or Kruskal-Wallis test was used for the comparison of two or more independent groups. In the correlation analysis, Spearman correlation analysis was applied depending on the distribution of data in correlation analysis. Significance was set at $p<0.05$ with a 95% confidence interval.

RESULTS

The mean age of the nurses was 35.73±6.80 years. They had worked for 15.30±7.78 years with 4.49±4.17 years of experience in the profession and in pediatric clinics, respectively. Of the nurses, 49.2% had bachelor's degrees and 95.0% had worked on rotation (Table 1).

The mean scores of the subscales of the PSCSN were 12.16±1.90 (occupational satisfaction), 22.6±2.89 (professional competence), and 74.06±6.69 (professional attitude and skills); the mean total score of the overall scale was 108.84±8.80 (Table 2). Age, gender, and work duration in the profession and in pediatric clinics were found not to affect the mean total score of the PSCSN ($p>0.05$). Compared to other nurses, the mean total score of the PSCSN was higher ($p<0.05$) for the nurses who had bachelor's degrees, who had higher degrees, who were in charge of the clinic, who had good communication with other healthcare staff, and who had willingly chosen this profession.

Table 1. Descriptive characteristics of the nurses (n=120)

Characteristics	n (%)
Age (years)	
22-29	20 (16.7)
30-39	64 (53.3)
40-49	34 (28.3)
50-55	2 (1.7)
Gender	
Male	4 (3.3)
Female	116 (96.7)
Educational Status	
Vocational Health School	16 (13.3)
Associate degree	41 (34.2)
Bachelor's degree	59 (49.2)
Master of Science degree	4 (3.3)
Working Duration (years)	
1-5	17 (14.2)
6-10	17 (14.2)
11-15	22 (18.3)
16-20	26 (21.7)
20-35	38 (31.7)
Working Duration in Pediatric Clinic (years)	
0-5	68 (56.6)
6-10	39 (32.5)
11-15	11 (9.2)
16 +	2 (1.7)
Working Position of the Nurse	
Clinic Charge Nurse	7 (5.8)
Shift Nurse	107 (89.2)
Other	6 (5.0)

Table 2.The mean scores of sub-dimensions of the PSCSN of the nurses

Sub-Dimensions	Mean± SD	Median (Min-Max)
Occupational Satisfaction	12.16±1.90	12.00 (8-17)
Professional Competence	22.6±2.89	22.00 (15-28)
Professional Attitude and Skills	74.06±6.69	74.00 (62-99)
Total Score	108.84±8.80	108.0 (89-129)

*The Professional Self-Concept Scale (PSCSN)

Table 3.The mean scores of sub-dimensions of the CCTDS of the nurses

Sub-Dimensions	Mean± SD	Median (Min-Max)
Analyticity	47.92±5.26	49.09 (34-58)
Open-mindedness	39.69±5.3	40.00 (30-66)
Inquisitiveness	41.20±6.62	41.25 (23-64)
Self-confidence	40.23±10.25	40.00 (16-79)
Truth-seeking	37.51±7.94	37.14 (15-39)
Systematicity	42.25±6.32	41.66 (20-60)
Total Score	248.82±23.76	248.25 (143-271)

*The California Critical Thinking Disposition Inventory (CCTDS)

The mean scores of the subscales of the CCTDS were as follows: 47.92±5.26 (analyticity), 39.69±5.33 (open-mindedness), 41.20±6.62 (inquisitiveness), 40.23±10.25 (self-confidence), 37.51±7.94 (truth-seeking), 42.25±6.32 (systematicity). The mean total score of the overall scale was 248.82±23.76 (Table 3). Age, gender and work duration of the nurses did not affect the mean total CCTDS score ($p>0.05$); it was determined that as the duration of education increased, the total CCTDS score increased and the mean total CCTDS score of the nurses who were in charge of the clinic was higher ($p<0.05$).

The mean score of all subscales and the total score of the PSCSN, except for occupational satisfaction, and the mean score of all subscales and the total score of the CCTDS, except for open-mindedness and truth-seeking, were found to be significantly and positively correlated ($p<0.05$) (Table 4).

DISCUSSION

Professional Self-Concept

Professional self-concept, which is defined as identification with the profession, has an important place in nursing because of its professional status and provision of quality services to the community (4-5, 13-15). The mean score of the PSCSN of the pediatric nurses in the present study was 108.84±8.80. Compared to this study, other studies (4, 14, 16) have reported higher PSCSN scores for nurses. This result can be explained by the inclusion of only pediatric nurses in this study, unlike other studies. Various studies that have determined professionalism using different scales have demonstrated that nurses have a good level of self-image (17) and that the level of professional self-concept is low among nurses (18).

Age, gender and work durations in the profession and in pediatric clinics did not affect the mean total score of the PSCSN in this study ($p>0.05$). However, some studies reporting on professionalism for nursing have noted that as age and work duration of the nurses increased, the score of professional self-concept increased (14,19-20). Differently, Öner et al. (17) have reported professional self-scores of 1st grade nursing students are higher than 4th grade nursing students.

Education plays a significant role on the professionalization of nursing. School training contributes to creating positive perception and thoughts about the profession and represents a major factor in the positive improvement of a professional identity (4,14,21). According to the study results the mean total scores of the PSCSN of pediatric nurses who were graduates with bachelor's degrees and higher degrees was found to be higher than those of other nurses. Similarly, several studies have shown that the educational status of nurses affected their professionalism and that nurses with a higher educational status had higher professional self-concept levels (18,22).

The mean total PSCSN scores of nurses who were in charge of the clinic, who had good communication with health care professionals, and who had willingly chosen the profession was higher than those of other nurses ($p<0.05$). The high PSSCN scores of the pediatric clinic responsible nurses can be associated with their taking responsibility for the management of the pediatric clinics where many critical decisions are made and the application is made. In addition, it has been stated that the clinical features studied affect the professional self-score (19,20). Sabancıoğulları and Doğan (4) similarly found that nurses who had willingly chosen their profession, who did not think about leaving the profession, who were considered to be hopeful about the future of the nursing and who recommended the profession to others had significantly higher mean total PSCSN scores. This result shows the importance of consciously choosing the nursing profession and the clinics where they work, and loving the profession. Other studies reported a higher level of professionalism in nurses who love their job, who do not want to change their profession, who think that their communication with team members is good, who are members of the professional association and who are in charge (14,19-20). Consistent with these results, it may be concluded that choosing the profession willingly and consciously, maintaining definite roles and responsibilities in the pediatric clinics and communicating with team members contribute to increasing professional motivation and favorably affect professional self-concept.

Table 4.The correlation between PSCSN and CCTDS of the nurses

	Satisfaction	Competence	Attitude and Skills	Total Score of the PSCSN	Analyticity	Open-mindedness	Inquisitiveness	Self-confidence	Truth-seeking	Systematicity	Total Score of the CCTDS
Satisfaction	1.000 -										
Competence	.018 .849	1.000 -									
Attitude and Skills	-.097 .292	**.617**** **.000**	1.000 -								
Total Score of the PSCSN	.136 .139	**.762**** **.000**	**.939**** **.000**	1.000 -							
Analyticity	073 .426	**374**** **.000**	**437**** **.000**	**472**** **.000**	1.000 -						
Open-mindedness	.095 300	-.057 537	017 .851	016 .861	114 .215	1.000 -					
Inquisitiveness	026 779	**481**** **.000**	**512**** **.000**	**542**** **.000**	**504**** **.000**	-015 .873	1.000 -				
Self-confidence	015 874	**587**** **.000**	**415**** **.000**	**491**** **.000**	**413**** **.000**	-177 .053	**680**** **.000**	1.000 -			
Truth-seeking	-009 922	-082 .372	-008 .927	-036 .695	-106 .250	**579**** **.000**	-091 .322	**-288**** **.001**	1.000 -		
Systematicity	026 779	**233*** **.010**	139 .131	179 .050	**427**** **.000**	**216*** **.018**	**434**** **.000**	**305**** **.001**	**181*** **.048**	1.000 -	
Total Score of the CCTDS	067 464	**448**** **.000**	**431**** **.000**	**468**** **.000**	**622**** **.000**	**433**** **.000**	**695**** **.000**	**558**** **.000**	**374**** **.000**	**693**** **.000**	1.000 -

* The Professional Self-Concept Scale (PSCSN), The California Critical Thinking Disposition Inventory (CCTDS)
**p<0.05

Critical Thinking

According to the study results the critical thinking level of nurses was determined to be mediocre (the mean total CCTDS score was 248.82±23.76). In other studies, nurses exhibited different levels of critical thinking (12,22-23). When the result is evaluated in terms of pediatric nurses who are expected to have a high level of critical thinking, it is thought that it may be affected by the pediatric clinic management style which expects nurses to carry out routine work and the expectation of working with excessive workload. In addition, individual self-development capability, different educational status and acceptance and receptiveness toward the nursing profession may be effective on the level of critical thinking.

In this study, age and work duration were not found to influence the critical thinking scores of nurses (p>0.05), whereas other studies have indicated that as age progresses and work duration increases, the critical thinking scores of the nurses also increase (20,23). The reasons for this may be the increased workload of nurses in pediatric clinics, high patient/nurse ratio, administrative factors, failure to develop a different perspective, and focus on routine care instead of taking a critical perspective.

Education plays an important role in increasing the level of critical thinking. As an individual's educational status increases, the individuals' level of critical thinking also increases (22, 24). In the present study, nurses with bachelor's degrees and higher degrees had a significantly higher mean CCTDS scores (p<0.05). Positive perceptions and thoughts about the profession are important factors for improving critical thinking. In this study, the mean total CCTDS score of the nurses who had willingly chosen their profession was significantly higher than those of other nurses (p<0.05). Öztürk and Ulusoy (25) reported that the mean total CCTDS scores of undergraduate nursing students and nursing students with a master of science degree who had willingly chosen the profession were high. Nurses with good communication are reported to have a high level of critical thinking (20,21).

The results of the study showed that pediatric nurses who had good communication with health care professionals had a higher average SCST score than the others ($p<0.05$). Critical thinking power was high in pediatric nurses who were able to establish healthy social relationships, which is one of the most important characteristics expected from pediatric nurses.

Pediatric clinic manager nurses who have to make fast and accurate decisions should have critical thinking skills. In the study results, it was noted that the critical thinkings scores of the manager nurses working in the clinic were significantly higher than the other nurses in the clinic ($p<0.05$). Erkuş (24) determined that manager nurses working in harmony with the team had high mean total CCTDS scores. Characteristics, such as recognizing problems and developing solutions for individuals working as management staff, improved the nurses' levels of critical thinking (12). This result may be related to that the manager nurses in pediatric clinic encountered problems more often and had to make faster decisions.

The mean score of all subscales and the total score of the PSCSN, except for satisfaction, and the mean score of all subscales and the total score of the CCTDS, except for open-mindedness and truth-seeking, were found to be significantly and positively correlated ($p<0.05$). Park et al. (21) stated that there was a positive relationship between professional self and critical thinking in their study, Barry et al. (26) defined a negative relationship in their work using different scales.

According to the results of the research, professional self-concept and critical thinking affect each other positively in pediatric nurses. As in all professions that struggle to develop a professional identity, pediatric nurses need to develop their thinking, questioning, research and analysis skills. By this way, pediatric nurses who can think critically can develop their professional identities effectively and accurately.

The mean score of all subscales and the total score of the PSCSN, except for occupational satisfaction, and the mean score of all subscales and total score of the CCTDS, except for open-mindedness and truth-seeking, were found to be significantly and positively correlated ($p<0.05$). Consequently, it was determined in this study that critical thinking in pediatric nurses ability is important for developing a professional self-concept and that educational and work status, voluntary choice of profession and communication with other health care professionals were effective in developing a professional self-concept and critical thinking skills. According to these results, educational programs for improving the professional self-concept and the critical thinking of all nurses, especially for pediatric nurses should be established and expanded.

Study limitations

The study was conducted with nurses working in the pediatric clinics. Therefore, the sample was limited to the number of nurses in the pediatric clinic of the hospital.

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