ACIBADEM
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SAĞLIK BİLİMLERİ DERGİSİ

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.

İçindekiler/*Contents*

RESEARCH ARTICLES / ARAŞTIRMA MAKALELERİ

Biochemistry and Molecular Biology / Biyokimya ve Moleküler Biyoloji

General and Internal Medicine / Genel ve Dahili Tıp

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

The Assessment of Mesenchymal Stem Cells Characteristics in Cultured Amniotic Fluid Cells

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ABSTRACT

Objectives: To evaluate the morphological characteristics, immunophenotypic features, osteogenic, adipogenic, and chondrogenic differentiation capacities of in-vitro cultured amniotic cells during the culture process based on mesenchymal stem cell (MSC).

Material/Method: This study used waste cells remaining after fetal karyotype determination with second-trimester amniotic cell culture. Cultured cells were morphologically evaluated daily. Selective subculture (SSC) was produced by the scraping method. Immunophenotypic features of primary and subculture amniotic cells were evaluated based on specific surface antigens. Specific growth mediums were used to assess their osteogenic, adipogenic, and chondrogenic differentiation abilities. Differentiation was confirmed using specific staining.

Results: Fifteen cases with 46,XY fetal cytogenetic analyses at 16^{+3}-19^{+5} gestational weeks were included in the study. Amniotic fluid cells were evaluated morphologically in three classes as Amniotic fluid specific cell-type(AF), Fibroblastoid cell-type(FB1, FB2), and Epithelioid cell-type(E). The first cell adhesions occurred in the first 24-48 hours(36%) of cell culture, while the first colonies within three days(82%). SSC was produced in AF-SSC(n=4) and FB2-SSC(n=6) directions by mechanical scraping. Primary amniotic fluid cells and AF/FB-SSCs were positive for MSC immunophenotypic markers CD29,CD73,CD166,CD44,CD49e,CD90, while negative for CD34,CD45, and HLA-DR. Cells were shown to have osteogenic (Alizarin Red-S) and chondrogenic (Alcian Blue) differentiation potentials based on histochemical staining, while adipogenic (Oil Red-O) differentiation was not obtained.

Conclusion: We believe that preliminary protocols and experiences to obtain MSCs from amniotic fluid-derived cells produced under routine prenatal diagnosis cell culture conditions can enable many promising pre-clinical/clinical studies and be the pioneer of "stem cell therapy applications" in many "incurable" diseases in the clinic.

Keywords: Amniocentesis, Cell morphology, Differentiation, Flow cytometry, Mesenchymal stem cell

Kültüre Amniyotik Sıvı Hücrelerinde Mezenkimal Kök Hücre Özelliklerinin Değerlendirilmesi

ÖZET

Amaç: Mezenkimal kök hücre (MKH) temelinde in-vitro kültüre amniyotik hücrelerin kültür işlemi sırasında morfolojik özelliklerini, immünofenotipik özelliklerini, osteojenik, adipojenik ve kondrojenik farklılaşma kapasitelerini değerlendirmek.

Materyal/Yöntem: 2. trimester amniyotik hücre kültürü ile karyotip tayini yapılmış "atık" hücreler kullanıldı. Kültür hücreleri, günlük morfolojik olarak değerlendirildi. Kazıma yöntemi ile selektif subkültür (SSC) üretildi. Primer ve subkültür amniyotik hücrelerinin immünofenotipik özellikleri, spesifik yüzey antijenlerine dayalı olarak değerlendirildi. Osteojenik, adipojenik ve kondrojenik farklılaşma yeteneklerini değerlendirmek için spesifik büyüme ortamları kullanıldı. Farklılaşma, spesifik boyama kullanılarak doğrulandı.

Bulgular: 16^{+3}-19^{+5} gebelik haftasında, fetal sitogenetik analizi 46,XY olan 15 olgu çalışmaya alındı. Amniyotik sıvı hücreleri morfolojik olarak Amniyotik sıvıya özgü hücre tipi(AF), Fibroblastoid hücre tipi(FB1, FB2) ve Epitelioid hücre tipi(E) olmak üzere üç sınıfta değerlendirildi. İlk hücre adezyonları hücre kültürünün ilk 24-48 saatinde (%36), ilk koloniler ise üç gün içinde (%82) meydana geldi. SSC'ler, AF-SSC(n=4) ve FB2-SSC(n=6) yönlerinde mekanik kazıma ile üretildi. Primer amniyotik sıvı hücreleri ve AF/FB-SSC'ler, MKH immünofenotipik belirteçleri CD29,CD73,CD166,CD44,CD49e,CD90 için pozitifti, CD34,CD45 ve HLA-DR için negatifti. Hücrelerin histokimyasal boyamaya dayalı osteojenik (Alizarin Red-S) ve kondrojenik (Alcian Blue) farklılaşma potansiyellerine sahip olduğu gösterilirken, adipojenik (Oil Red-O) farklılaşma elde edilemedi.

Sonuç: Rutin prenatal tanı hücre kültür koşullarında üretilen amniotik sıvı kökenli hücrelerden MSC elde etmeye yönelik oluşturulan öncül protokoller ve elde edilen deneyimlerin, gelecek vaadeden pek çok preklinik/klinik araştırmaya olanak sağlayabileceği ve klinikte pekçok "çaresiz" hastalıkta, "kök hücre tedavisi uygulamaları"nın öncüsü olabileceği inancındayız.

Anahtar Kelimeler: Amniosentez, Hücre morfolojisi, Farklılaşma, Flowsitometri, Mesenkimal kök hücre

Stem cells can constantly renew themselves and differentiate into various tissues, and they can differentiate into cell types of mesodermal, ectodermal, and endodermal origin under specific conditions (1).

Due to the increasing application areas of stem cell researches in medicine, it has become necessary to search for stem cell sources that can be used in human applications. Fetal mesenchymal stem cell (MSC) is one of the sources determined from these studies. Amniotic cells are fetal cells that have been routinely used to diagnose genetic diseases; recent publications identify amniotic fluid-derived MSCs as potent candidate cells with particular advantages in the cell therapy approach due to their biological and genetic characteristics (2-5).

This study aimed to investigate the MSC potential of amniotic fluid cells, which were in the "waste" position after genetic analysis, and evaluate the morphological characteristics, immunophenotypic characteristics, and osteogenic, adipogenic, chondrogenic differentiation capacities of the cells during the culture process.

MATERIAL AND METHOD

Amniotic Fluid-derived Stem Cell Isolation and Cell Culture

Cell Source

Second-trimester amniotic fluid cells were used in the study. Cells were obtained from cultured cells "waste" of 15 prenatal diagnosis cases who underwent routine amniocentesis for genetic diagnosis. Fetuses with malformations detected in fetal ultrasonography and amniotic fluid cells with hemorrhagic features were excluded from the study. The local medical ethics committee (Decision no: OMU Rectorate projects, T-393, T-394) approved the study in accordance with human and animal rights and complied with the principles of the Helsinki Declaration. Informed consent was obtained before collecting samples from all patients.

Cell Culture

The 3ml cell debris obtained after the centrifugation of the amniotic fluid samples for 10 minutes at 1500rpm was suspended with Bio-AMF-1 (Biological Industries, Kibutz Beit Haemek) containing 100U/ml penicillin, 0.1mg/ml streptomycin, and 1L Glutamine (Gibco) and inoculated into three different 25 cm² flasks (Nunc, Rochester, MN).

The flasks were named P01, P02, and P03. After seven days, a fresh medium was added to the cells adhering to the flask surface. Once the adherent cells filled the flask, the P01-flask was used for fetal karyotype determination. P02 and P03 flasks remaining in the waste cell state were used in further studies.

Cell Morphology

All flasks were examined under an inverted microscope (OLYMPUS CKX41) for morphological characteristics during the culture and subculture process.

Karyotyping

Fetal cytogenetic analysis was performed at P01-flask (n=15).

Immunophenotyping

In the P02-flask (n=15), adherent cells were removed by trypsinization with trypsin/EDTA C 10X solution (Bio. Ind., 03-053-1) once the flask was filled. Cells were washed twice with Phosphate Buffer Saline (PBS). 100µl of amniotic fluid samples were placed in the tubes with a cell concentration of 1×10^6/ml. The tubes were vortexed by adding monoclonal antibodies in the appropriate titrations (5-10µl). They were incubated for 15 min at 4°C and in the dark. Then 1ml of washing solution (PBS + 0.1% Na azide) was added to the tubes and centrifuged at 1400rpm for 5 minutes. 0.5ml of wash solution was added to the cell precipitate again and read on the FACSCalibur (Becton Dickinson, Biosciences) flow cytometer and analyzed in the "Cell Quest Software" program [Becton Dickinson immunocytometry system, Mac OS X 10.3.6 (7R28)]. Samples prepared using autofluorescence and appropriate isotypic control were used as a negative control. Quadrants or histogram markers were adjusted relative to negative controls.

Selective Subculture (SSC)

Cell colonies adhered to the P03-flask were morphologically (OLYMPUS CKX41) monitored daily. The mechanical scraping method was used for a subculture (BD FalconTM cell scraper). Once the selected permanent colonies filled the flask, they were trypsinized with trypsin/EDTA C 10X solution (Bio. Ind., 03-053-1) and grown in two separate flasks, one for immunophenotyping and the other for differentiation studies.

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Immunophenotyping in Selective Subculture (SSC)

Cells obtained from SSC-flasks (P13a) (n=10) were evaluated as immunophenotypic.

Differentiation Protocol and Histochemical Staining

Osteogenic Differentiation

In osteogenic differentiation studies, cells grown in an in-vitro culture medium were studied by a method in accordance with the literature information of Pittenger et al. (6). Trypsinized cells were treated with osteogenic medium [DMEM-LG (Euroclone Ltd.,UK) containing 10% Fetal bovine serum (FBS)(Euroclone Ltd.,UK), dexamethasone (100nM,Sigma,USA), beta glycerophosphate (10mM,Sigma,USA) and ascorbic acid (0,2mM,Sigma,USA)] after approximately 1 week of culture step. The medium was freshened every 3-4 days for 21 days. At the end of the 21st day, it was stained with "Alizarin Red-S" (6-12).

Adipogenic Differentiation

In adipogenic differentiation studies, cells grown in an in-vitro culture medium were studied by a method in accordance with the literature information of Pittenger et al. (6). Trypsinized cells have waited until they filled up the flask. Then, the medium was refreshed with adipogenic medium [DMEM-LG (Euroclone Ltd., UK) containing 10% FBS (Euroclone Ltd., UK), dexamethasone (1µM, Sigma,USA), indomethacin (60µM, Sigma,USA), 3-isobutyl-1-methylxanthine (IBMX) (500µM, Sigma,USA) and insulin (5µg/ml, Sigma, USA)] every 3-4 days and stained with "Oil Red-O" on day 21 to show the presence of adipogenic differentiation (6-9,11-13).

Chondrogenic Differentiation

Chondrogenic differentiation studies were done by a method according to the literature information of Pittenger et al. (6). Trypsinized cells were placed in 2 separate 15-ml polypropylene centrifuge tubes (2.5x10^5 cells), centrifuged at 1000rpm for 5 minutes, and formed into pellets. The pellet was incubated for 24 hours at 37°C, 5% CO2. Then, it was treated with chondrogenic medium [DMEM-HG (Euroclone Ltd.,UK) containing dexamethasone (100nM,Sigma,USA), TGF-B3 (10ng/ml,Peprotech,USA), ascorbic acid (50µg/ml,Sigma,USA), ITS+Premix (50mg/ml 500 B&D Biosciences)] and the medium was refreshed every 3-4 days for 21 days. At the end of the 21st day, 5µm thick "frozen" sections were taken with a semi-automatic

rotating arm microtome (RM2125RT Leica), and the preparations were stained with "Alcian Blue" and "Hematoxylin/Eosin." (8,14-16).

RESULTS

Amniotic Fluid-derived Cell Source and Karyotyping

Fifteen male (46,XY) amniocentesis cases with a gestational age of 16^{+3}-19^{+5} weeks, maternal age between 24-44 years, were included in the study.

Cell Culture and Cell Morphology

Cells seeded from amniotic fluid in 3 separate flasks under sterile conditions consisted of amniocytes of different maturity (young and old). Initial cell adhesions were observed within the first 24-48 hours of primary amniotic fluid cell culture. Adhesion was observed in 20%, 36%, and 82% of flasks at 24, 48, and 72 hours, respectively. The first colonies were observed on the 3-5th day, and on the 8th-11th days, the cell density filled 2/3 of the culture dish.

During the 2-week follow-up period, colonies were observed in 3 cell types: Amniotic fluid specific cell-type (AF), Fibroblastoid cell-type (FB1, FB2), and Epitheloid cell-type (E).

The fibroblastoid-type cells were spindle-shaped cells parallel to each other. The long and thin structure of FB1 cells was more homogeneous than FB2 cells. AF-type cells were non-tightly organized, round-shaped, polygonal cells, whereas epithelioid-type cells were tightly organized, forming small colonies, and had a rounded, sharp-edged, manlike morphology.

At the initial stage of culture, the cell population was heterogeneous. AF-type cells were observed throughout the culture process; E-type cells were significantly reduced after a short time. FB1-type cells emerged relatively late in the culture process, on average ten days (Fig.1).

Immunophenotyping

On days 15-18 of the primary cell culture (P02) (n=15), in immunophenotyping, CD90, CD73, CD166, CD49e, CD44, CD29, HLA-ABC were positive, CD34, CD45, HLA-DR were negative. "Dot-plot" and "histogram graphs" of all cases were constituted. In 10 cases, cell surface antigen with CD14 antibody was also studied and found negative (Table.1) (Fig.2).

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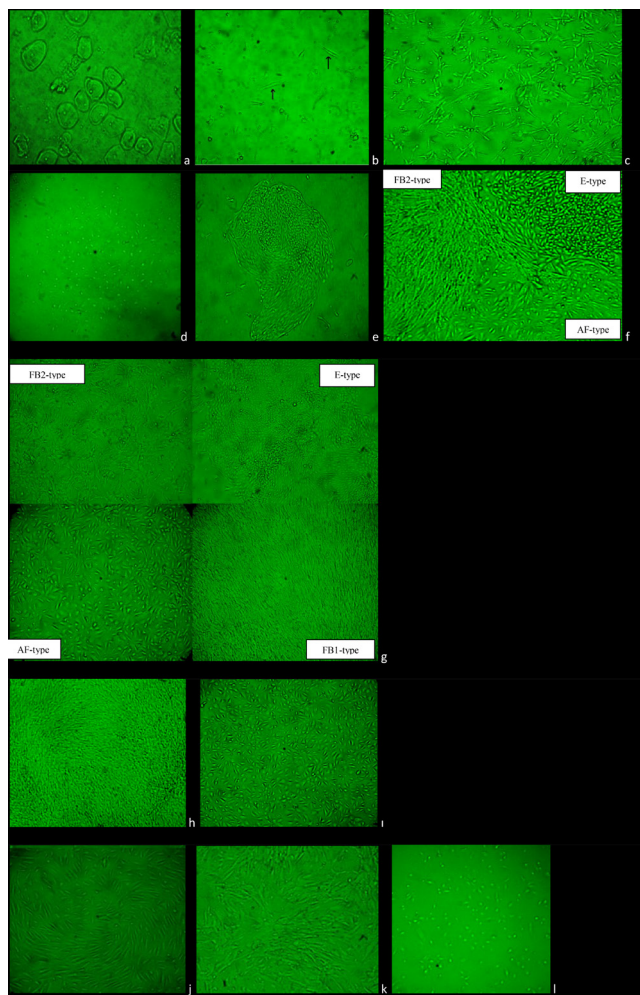
Figure 1: Amniotic fluid cell morphology; a- First-day appearance of amniotic fluid cells in culture (OLYMPUS CKX41, 10X); b- First 24-48 hours, first cell adhesions (OLYMPUS CKX41, 10X); c- FB2-type cell adhesions (first colonies) in the first 3-5 days (OLYMPUS CKX41, 4X); d- AF-type cell adhesions (first colonies) in the first 3-5 days (OLYMPUS CKX41, 4X); e- Epithelioid-type cell adhesions (first colonies) in the first 3-5 days (OLYMPUS CKX41, 4X); f- Cell types in amniotic cell culture (OLYMPUS CKX41, 10X); g- Cell types in amniotic cell culture (OLYMPUS CKX41, 10X); h- AF selective subculture image (Olympus CKX41, 10X); I- FB2 selective subculture image (Olympus CKX41, 10X); j- Post-trypsinization images of AF selective subcultures (Olympus CKX41, 10X); k- Image of FB2 selective subcultures after trypsinization (Olympus CKX41, 10X); l- AF selective subcultures degenerated (Olympus CKX41,10X)

Selective Subculture (SSC)

Adhering cells in the P03-flask were monitored daily and mechanically scraped to form SSCs (BD FalconTM cell scraper) specific to a single cell (FB2/AF) colony. E-type cells could not be included in the study because they disappeared rapidly in culture. In some cultures, mechanical scraping could not be achieved. Out of 10 cases, AF-type SSC was done in 4 and FB2-type in 6. When the culture flask was nearly full, the SSC-flask was trypsinized with trypsin/EDTA C 10X solution (Bio.Ind., 03-053-1) and grown in two separate flasks. FB2/AF-SSCs retained their morphological features after trypsinization. "Embryoid body"-like spheroid structures were observed in AF-SSCs. While FB2-SSCs ensured culture continuity after the third passage, AF-SSCs degenerated at the same time (Fig.1).

Table 1: Immunophenotyping Protocol	
Tube No	**Antibody (Becton Dickinson, Biosciences)**
1	CD 45 (FITC) / (Bazen CD 14) (PE)
2	Ig G1κ (FITC) / Ig G1κ (PE) (isotypic control)
3	CD 34 (FITC) / CD 73 (PE)
4	HLA-DR (FITC) / CD 166 (PE)
5	/ CD 29 (PE)
6	/ CD 44 (PE)
7	/ CD 90 (PE)
8	/ CD 49e (PE)
9	HLA-ABC (FITC) /
10	Autofluorescent control (amnion cells were treated in the same way without staining with any monoclonal antibody)
"Fluorescein isothiocyanate" (FITC), "Phycoerythrin" (PE), "Cluster of Differantiation" (CD), Immunoglobulin G1-kappa (Ig G1κ)	

Selective Subculture (SSC) Immunophenotyping

10 cases underwent SSC in the P13a-flask were immunophenotypically determined as CD90, CD73, CD166, CD49e, CD44, CD29, HLA-ABC positive, CD34, CD45, HLA DR negative. Cell surface antigen with CD14 antibody was studied in 3 cases and found negative. "Dot-plot" and "histogram graphs" of all cases were constituted (Table.1) (Fig.2).

Differentiation

Adipogenic and Osteogenic Differentiation

FB2-SSCs could be done in a total of 8 cases. Differentiation studies were initiated at passage-2 in 4 cases, at passage-3 in 3 cases, and passage-4 in 1 case. In FB2-SSCs, in the wells in which differentiation study with the osteogenic medium was initiated, accumulation of white material also seen macroscopically, indicating calcium accumulation, was observed and osteogenic differentiation was demonstrated with Alizarin Red-S in all cases in different passages. However, in adipogenic differentiation processes, intracytoplasmic lipid accumulation could not be demonstrated with Oil Red-O, and adipogenic differentiation was not detected. In AF-SSCs, early degeneration of cells was observed in 5 cases. One heterogeneous case was included in the study in passage-1, and while osteogenic differentiation was detected in this case, adipogenic differentiation was not observed (Table.3) (Fig.3).

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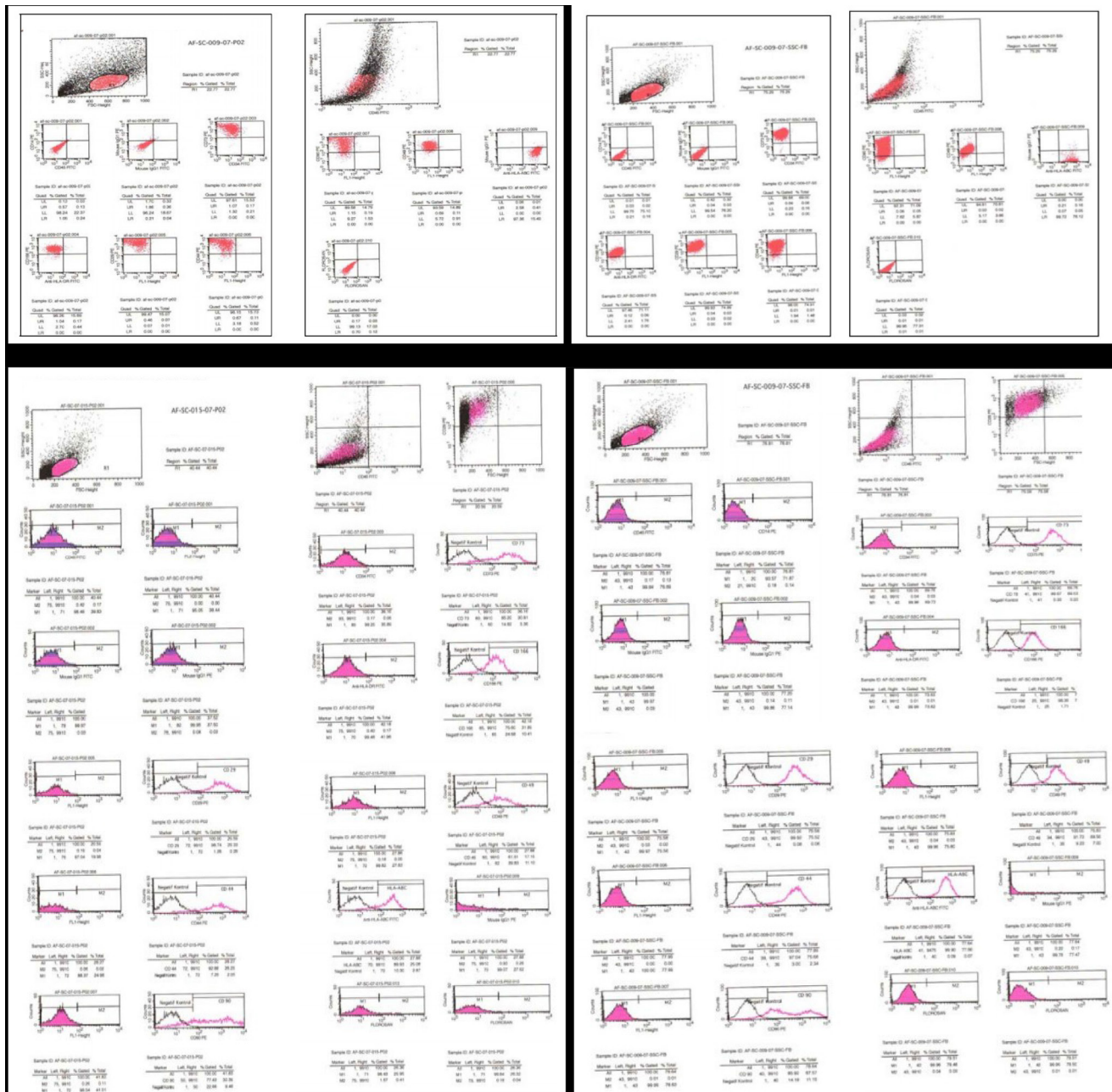
Figure 2: Example Dot-Plot and Histogram graph for primary cell culture and SSC

Chondrogenic Differentiation

Cartilage-like differentiation was detected with Alcian Blue and Hematoxylin/Eosin, in a total of 11 cases, 8 in FB2-SSCs, 2 in AF-SSCs, and 1 in heterogeneous character (Table.3) (Fig.3).

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0, and all data were expressed as descriptive statistics and percentages. $P < 0.05$ was considered statistically significant. Normality analyzes of the surface marker data of the immunophenotyped primary cultured cells (Po) and AF/FB2-SSCs were first performed. Since the data did not show a normal distribution, three groups (PO/AF/FB) were compared using the non-parametric statistical Kruskal-Wallis method. $P < 0.05$ was accepted as the level of significance.

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Table 2: Primary Cell Culture and SSC "Dot-plot" Immunophenotyping Results

Primary cell culture "Dot-plot" Immunophenotyping results

Case code	CD73	CD90	CD166	CD49e	CD44	CD29	HLA-ABC
1	96.85	94.06	99.52	99.01	99.73	100.00	99.82
2	99.60	93.57	99.62	98.29	99.58	100.00	99.79
3	99.55	84.95	99.64	99.21	99.80	100.00	100.00
4	96.30	84.18	99.18	98.62	100.00	100.00	99.85
5	98.51	89.34	99.76	98.20	99.95	100.00	99.87
6	97.63	87.43	99.77	99.61	100.00	100.00	100.00
7	89.77	82.44	93.13	87.74	97.69	99.30	97.84
8	100.00	-	98.15	98.07	99.87	99.94	99.95
9	98.68	90.73	97.30	94.28	96.82	99.93	99.94
10	99.16	83.00	98.89	97.21	99.76	99.91	98.89
11	98.43	96.97	88.08	96.11	98.66	100.00	99.08
12	85.93	37.09	90.65	75.93	99.21	98.26	97.47
13	84.97	80.56	46.66	63.41	96.76	98.45	80.95
14	93.36	78.86	90.53	62.73	98.75	99.68	92.76
15	99.38	90.04	94.78	89.73	98.53	99.94	98.14
Mean	95.87	83.80	93.04	90.54	99.01	99.69	97.62

SSC "Dot-Plot" Immunophenotyping results

Case code	CD73	CD90	CD166	CD49e	CD44	CD29	HLA-ABC
001 AF	96.64	29.80	98.14	96.64	99.44	99.73	98.06
006 AF	98.30	26.05	99.20	98.92	99.98	100.00	99.67
008 FB2	99.84	98.89	98.48	99.53	98.84	100.00	98.20
009 FB2	99.77	92.37	97.58	94.84	98.06	99.97	99.93
010 AF	99.52	33.51	99.59	96.60	99.86	99.95	99.93
011 FB2	99.70	90.28	95.91	99.07	95.58	99.96	98.42
012 FB2	98.92	89.41	95.20	84.54	99.24	99.81	87.38
013 AF	99.59	76.20	99.17	94.51	99.90	99.68	98.84
014 FB2	99.81	75.62	98.11	91.74	99.53	99.99	99.25
015 FB2	95.25	87.53	96.70	91.97	98.44	99.82	97.35
Mean	98.73	69.96	97.80	94.83	98.88	99.89	97.70

Table 3: Summary of Tri-lineage Differentiation

Case Code	Differentiation Code	SSC	Passage	Adipogenic Differentiation	Osteogenic Differentiation
011	OS-1	FB2	P2	Not observed	Positive
011	OS-1	FB2	P4	Not observed	Positive
012	OS-2	FB2	P2	Not observed	Positive
016	OS-3	Heterogenous	P1	Not observed	Positive
008	OS-4	FB2	P3	Not observed	Positive
009	OS-5	FB2	P2	Not observed	Positive
009	OS-5	FB2	P3	Not observed	Positive
010	OS–6	AF	P2	no cell proliferation, inefficacious work	
010	OS–6	AF	P4	no cell proliferation, inefficacious work	
013	OS-7	AF	P4	no cell proliferation, inefficacious work	
013	OS-7	FB2	P2	Not observed	Positive
006	OS-8	AF	P3	no cell proliferation, inefficacious work	
014	OS-9	AF	P2	no cell proliferation, inefficacious work	
014	OS-9	FB2	P3	Not observed	Positive

Case Code	Differentiation Code	SSC	Chondrogenic differentiation
011	OS-1,1	FB2	Positive
011	OS-1,2	FB2	Positive
012	OS-2	FB2	Positive
016	OS-3	Heterogenous	Positive
008	OS-4	FB2	Positive
009	OS-5	FB2	Positive
010	OS-6	AF	Positive
013	OS-7	AF	Positive
015	OS-8	FB2	Positive
014	OS-9	FB2	Positive
010	OS-10	FB2	Positive

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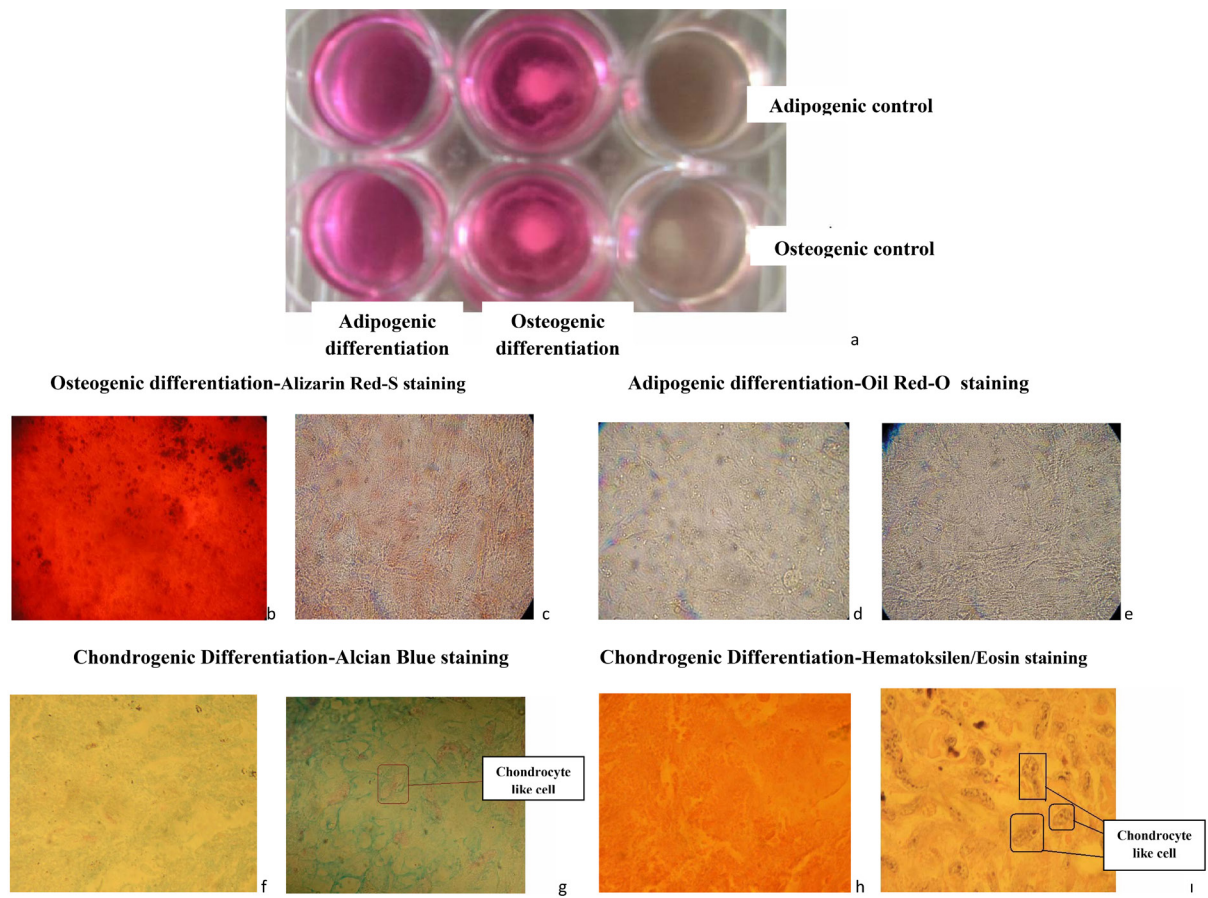
Figure 3: Tri-lineage differentiation studies; a- Macroscopic observation of osteogenic differentiation; b- Osteogenic differentiation -Alizarin Red-S staining case (Positive) (Olympus CKX41, 40X); c- Osteogenic differentiation- Alizarin Red-S staining control (Negative) (Olympus CKX41, 40X) ; d/e- Adipogenic differentiation-Oil Red-O staining case (Negative), control (Negative) (Olympus CKX41,40X); f- Chondrogenic Differentiation-Alcian Blue staining control (Negative) (OlympusBX51,100X); g- Chondrogenic Differentiation-Alcian Blue staining case (Positive) (OlympusBX51, 100X);h- Chondrogenic Differentiation-Hematoxylin/Eosin staining control (Negative) (OlympusBX51,100X); ı- Chondrogenic Differentiation-Hematoxylin/Eosin staining case (Positive) (OlympusBX51, 100X)

DISCUSSION

This study aimed to obtain MSCs from amniotic fluid-derived cultured cells routinely processed in laboratory conditions. In order to prevent possible maternal cell contamination and show the fetal origin of cultured MSCs, hemorrhagic amniotic fluid samples were not included in study, and only 46,XY cultures were used, as in some studies in the literature (2,3).

Morphological evaluation of amniotic fluid-derived cells under culture conditions is available in several studies (17-20). In the literature, some studies classify amniotic fluid cells into two as adherent and non-adherent cells and adherent and colony-forming cells into three as E-Type,

AF-Type, F-Type under routine culture conditions (21). It is stated that AF-Type and E-Type cells were observed in the early stages of the culture, E-Type cells significantly decreased during the culture process, and F-Type cells appeared in the later culture stages. AF-Type cells are thought to be originated from fetal membrane and trophoblasts, F-Type cells from fibrous connective tissue and dermal fibroblasts, E-Type cells from fetal skin and urinary system (13,18,21).

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Our study monitored the cell morphology from the first seeding of the cell culture, and images were evaluated on the 1st, 3rd, fifth days, first week, second week, and after trypsinization. Adherent cells were evaluated in three classes as AF-type, Fibroblastoid cell type (FB1, FB2), and E-type. FB1-type and FB2-type were determined as spindle-shaped cells parallel to each other. FB1-type cells had a long and thin structure and were much more homogeneous than FB2-type cells. AF-type cells were noted as non-tightly organized, round-shaped, and polygonal cells. E-type cells were determined to be very tightly organized, form small colonies, and be rounded and sharp-edged cells forming islets.

In our cultures, amnion cells adhered to the culture plates in the first three days (82%). The first colonies formed on the 3-5th day, and the cell density filled 2/3 of the culture plate on the 8th-11th days. At the initial stage of culture, a heterogeneous cell population, FB2, AF, and E-type, was demonstrated. While AF-type cells persisted throughout the culture process, E-type cells showed a significant decrease after a short time. FB1-type cells appeared relatively late in the culture process, with an average of 10 days.

In the literature, it is stated that normal fetus-derived amnion cells adhered to the culture plates on the 3th-4th day, whereas in the presence of fetal malformation, the cells growth rate was faster, and they started to adhere to the culture plates in less than 24 hours and had different cell morphologies (17,22). Pregnancies with fetal malformations detected in ultrasonography were not included in this study.

The "mechanical scraping" method is a practical method that can provide specific clone selection in cell cultures. Our study produced selective subcultures in parallel with the morphological evaluation. Initially, subculture studies of all three cell types were carried out. However, subculture studies could only be performed with AF-type and FB2-type cells since FB1-type cells appeared relatively late in the culture process and were contaminated with other cells, and E-type cells were reduced and disappeared. The selected cell type was allowed to proliferate in the subculture, while other cells were removed by mechanical scraping, repeated daily. Similar studies in the literature are relatively few (4,5). In some studies, a two-step culture method has been developed to obtain MSCs (13,20). In other studies, cells expressing membrane receptor c-kit (CD117) were obtained by positive selection (2,12,20).

We observed that the main morphological structure of the specific cell type was preserved after trypsinization in selective subcultures. After trypsinization, broad-based and non-dividing cells were observed in AF-type cells, which failed to proliferate, especially after the third passage. F-type cells, on the other hand, proliferated rapidly in repetitive passages.

We showed that amniotic cells grown in our routine amniotic cell culture conditions highly expressed MSCs surface antigen in primary culture cells and in their selective subcultures. This result was consistent with previous MSC immunophenotype results (2-4,7-9,11,13,23).

As stated in previous studies, fibroblastoid morphology similar to bone marrow-derived MSCs was detected in FB2-SSC flasks (11,15,23). It has been suggested that MSCs are FB-type amnion cells because of the rapid proliferation of FB-type cells in cultures, their more stable passage continuity, their structures being fibroblastoid-like MSCs originating from the bone marrow, and their immunophenotypic and differentiation characteristics (13).

In AF-SSC flasks, "embryoid body"-like colonies similar to spheroid structures were observed (24). In the literature, it has been reported that these cells express high levels of embryonic stem cell markers such as 0ct-4, Nanog, and SSEA-4 (24). Since selective clones could not be obtained from spheroid colonies in AF-SSC bottles in our study, Oct-4 and similar embryonic stem cell markers could not be studied, but MSC immunophenotypic markers were shown to be expressed. We thought that the MSC marker expression in AF-SSC flasks might be due to a small number of MSCs with strong colonization properties and forming spheroid structures.

In this study, cartilage-like differentiation was detected in a total of 11 cases. Eight of the cases had FB2-SSC, 2 had AF-SSC, and 1 had heterogeneous character. The chondrogenic study protocol was based on literature studies (6,25). In the literature, it has been stated that for chondrogenic differentiation, in-vitro MSCs must first be condensed, followed by cartilage-like differentiation (25). In our study, three-dimensional pellet formation was first provided to ensure in-vitro chondrogenic differentiation. After using the differentiation medium, sections were taken from the pellet, and cartilage differentiation was demonstrated in the preparations with "Alcian Blue" and "Hematoxylin/Eosin" staining (8,15).

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Our osteogenic and adipogenic differentiation studies were initiated in the second passage in 4 of 8 FB2-SSC cases, the third passage in 3, and the fourth passage in one. One case with heterogeneous cell character was studied at passage-1. In 5 cases in which AF-SSC was initiated, differentiation studies could not be performed due to early degeneration of cells. In our study, differentiation was detected in all culture wells in which differentiation study was started with osteogenic medium, and it was shown with "Alizarin Red-S" staining (2,6-9,11,12). In the literature, studies indicate that osteogenic differentiation is achieved when the fibroblastoid-type is the predominant cell type in amniotic fluid cell cultures, and this differentiation is demonstrated by the expression of osteocalcin (11).

Cells stimulated with adipogenic medium simultaneously with osteogenic differentiation were stained with Oil Red-O to show the presence of differentiation. However, intracytoplasmic lipid accumulation, indicative of adipogenic differentiation, was not observed in any cases. There are studies in the literature showing the adipogenic differentiation capacity of MSCs obtained from amniotic fluid (2,7,9-13,15,20). Bossolasco et al. (11) used indomethacin approximately three times and insulin two times more in their study; they also used 0.5μM hydrocortisone, 60mM indomethacin, 100ng/ml insulin. On the other hand, Kim et al. (15) used approximately three times higher doses of indomethacin and 100 times lower doses of insulin and medium containing epidermal growth factor and FBS. De Coppi et al. (2), Delo et al. (12) used 3-isobutyl-1-methylxanthine (IBMX) and insulin two times more in their studies and obtained amniotic fluid-derived cells by c-kit positive cell selection. The stem cell rate obtained in our study may also have been insufficient for adipogenic differentiation. In the literature, there are studies using 20% FBS and 4ng/ml fibroblast growth factor (10,13,20) and 10% FBS and 20μg/ml endothelial growth factor (7,9) in MSC studies. These growth factors were not used in our study. Our study's inability to show adipogenic differentiation may be due to inadequate use of the protocol applied and chemicals and growth factors applied at different doses.

Limitations

Our study has some strengths and limitations. Although the number of patients included in the study is relatively small, it is similar to the related studies in the literature. This study was performed under "routine" laboratory conditions and achieved its goals based on mesenchymal stem cells, excluding adipogenic differentiation. Adipogenic differentiation capacity could not study with different protocols because of a one-time study. Osteogenic and chondrogenic differentiation achieved and mesenchymal stem cell markers demonstrated in both primary and selective subcultures.

CONCLUSION

This study demonstrated the "Mesenchymal Stem Cell" character of amniotic fluid-derived cells produced under "routine" laboratory culture conditions on an immunophenotypic basis and determined their osteogenic and chondrogenic differentiation potentials. Morphological evaluation data suggested that amniotic fluid MSC originated from a unique cell group (FB2-type cells) within the heterogeneous cell population of amniotic fluid.

The data obtained from similar studies in the literature and our study showed that amniotic fluid-derived MSCs could differentiate effectively in-vitro. The sufficient differentiation seen in 2 different cell lines (osteogenic and chondrogenic) in our study suggested that the fetal cell culture conditions in "routine" laboratory studies provide an advantage for amniotic cell-derived MSC isolation and a significant convenience for subsequent similar studies.

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

Investigation of *O*-Alkyl/*O*-Alkenyl Glycerolipid Ratios in Erythrocyte Lysates of Patients with Obstructive Sleep Apnea

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ABSTRACT

Background: Vulnerabilities of plasmalogens in erythrocyte membrane to hypoxic conditions and alteration induced by sleep restriction make them potential biomarkers for the evaluation of sleep apnea related sleep disorders.

Objective: We aimed to investigate and to compare ratios of alkyl/alkenyl glycerolipids of erythrocyte membranes (representing plasmanyl/plasmenyl plasmalogens) between controls and patients with sleep apnea and to evaluate possible differences, if any, which could be considered as a diagnostic tool.

Material and methods: The patients underwent polysomnography and categorized according to the severity of sleep apnea using Apnea-Hypopnea Index (AHI). Phospholipids in erythrocyte lysates were hydrolyzed by phospholipase C and the acylgroups were saponified. Then the *O*-alkyl/*O*-alkenyl glycerolipids were separated by thin-layer chromatography (TLC). Densitometric image analyses were performed on the lipid spots of TLC plates and the ratios were determined.

Results: No significant correlation was observed between the alkyl/alkenyl glycerolipid ratios of the eryhtrocyte lysates of sleep apnea patients and that of controls.

Conclusion: Results of this study warrants reinvestigation of alkyl/alkenyl glycerolipid ratios in erythrocytes of patients with sleep apnea, with each subjects sampled before and after the treatment of sleep apnea to better understand the potential of this ratio as a diagnostic tool.

Keywords: circadian rhythm; erythrocyte; obstructive sleep apnea; plasmalogen; hypoxia; thin-layer chromatography

Obstrüktif Uyku Apneli Hastaların Eritrosit Lizatlarında *O*-Alkil/*O*-Alkenil Gliserolipid Oranlarının Araştırılması

ÖZET

Giriş: Eritrosit membran plazmalojenlerinin uyku apnesinin yol açtığı hipoksik şartlara ve uyku bozukluklarına bağlı değişimlere duyarlı olması, uyku apnesine bağlı uyku bozukluklarının değerlendirilmesinde onları potansiyel bir biyobelirteç yapmaktadır.

Amaç: Uyku apnesine bağlı uyku bozukluğu olan hastalarda ve kontrollerde eritrosit alkil/alkenil gliserolipid oranlarını (plasmanil/plasmenil plazmalojen) araştırarak karşılaştırmak ve varsa muhtemel farklılıkları tanı vasıtası olarak değerlendirmek.

Materyal ve metod: Hastalara polisomnografi uygulandı ve Apne-Hipopne İndeksi (AHI) kullanılarak uyku apnelerinin şiddetine göre kategorize edildiler. Eritrosit lizatındaki fosfolipidler fosfolipaz C ile hidrolize edilerek açil grupları saponifiye edildi. *O*-alkil/*O*-alkenil gliserolipidler ince tabaka kromatografisi (TLC) ile ayrıldı. TLC plakaları üzerindeki lipid bantları dansitometrik olarak analiz edilerek oranlar belirlendi.

Sonuçlar: Uyku apneli hastaların eritrosit lizatlarında *O*-alkil/*O*-alkenil gliserolipidler oranları ile kontroller arasında istatiksel olarak anlamlı bir korelasyon bulunamadı.

Sonuç: Bu çalışmanın sonuçları, uyku apneli hastaların eritrosit lizatlarında *O*-alkil/*O*-alkenil gliserolipidler oranlarının tedavi öncesi ve tedavi sonrası dönemde tespit edilerek karşılaştırılmasının, bu oranın bir tanı vasıtası olarak potansiyelinin daha iyi değerlendirilebilmesi için gerekli olduğuna işaret etmektedir.

Anahtar kelimeler: sirkadiyen ritim; eritrosit; obstrüktif uyku apne; plazmalojen; hipoksi; ince tabaka kromatografisi

Obstructive sleep apnea (OSA) is a sleep disorder pathogenesis of which is thought to be connected with intermittent hypoxia during period of apnea or hypopnea inducing oxidative stress and systemic inflammation with cardiovascular consequences (1). There have been some works indicating an association between sleep apnea and circadian rhythm disturbances. Hypoxia in OSA has been reported to cause an increase of HIF-1α which in turn disrupts the circadian rhythm in vitro (2). The plasmalogens are among the most altered plasma lipids as a function of sleep restriction (3-5).The authors related the metabolite changes to PPARα and more generally peroxisome involvement in sleep restriction (4).

Plasmalogens are a class of membrane glycerophospholipids. Both choline and ethanolamine glycerophospholipids in mammalian tissues consist of three subclasses; 1,2-diacyl-sn-glycero-3-phosphocholine (or ethanolamine), 1-alkyl-2-acyl-sn-glycero-3-phosphocholine (or ethanolamine), 1-alk-1'-enyl-2-acyl-sn-glycero-3-phosphocholine (or ethanolamine). Those glycerophospholipids with alk-1-enyl groups at the sn-1 position of the glycerol are also referred to as plasmalogens (choline plasmalogens, ethanolamine plasmalogens) (6). In the course of synthesis in peroxisomes, plasmanyl plasmalogens which include an alkyl chain at sn-1 position of glycerol backbone are oxidized by a desaturase to yield the vinyl ether double bond in alkenyl chain of plasmenyl plasmalogens (7). Therefore, alkyl glycerolipids are considered as biosynthetic precursors of alkenyl glycerolipids (8) and as a consequence, alkyl/alkenyl glycerolipid ratio could be indicative of plasmalogen synthesis. We hypothesized an alteration in plasmalogen content of erythrocytes of patients with obstructive sleep apnea due to hypoxia and/or sleep disorder related circadian disturbances. Besides, plasmalogen levels in erythrocyte lysates are used as an diagnostic tool in inherited peroxisomal diseases (e.g. Rhizomelic chondrodysplasia punctata, Zellweger disorder) (9). To this end, we aimed to compare, for the first time, alkyl/alkenyl glycerolipid ratios in erythrocyte lysates of control and patients with sleep apnea associated sleep disorder groups and to evaluate the ratio as a potential biomarker for the diagnosis of obstructive sleep apnea conditions.

MATERIALS AND METHODS

Subjects and Experimental Design
The procedures were performed in accordance with the guideline set by İnönü University, Malatya Clinical Research Ethical Committee (Protocol number: 2016/198). The patient group consisted of 30 (22 male or 8 female) subjects. aging between 25-60. The control group included 30 age interval-matched subject (12 male and 18 female).

Inclusion criteria for the subjects: Subject is male or female between the age of 25 and 60 and provides written informed consent. Patient subject is having obstructive sleep apnea syndrome (OSAS). Exclusion criteria for subjects: Subject has an genetic disease, currently using CPAP machine, a history of malignancy or any autoimmune disease, undergone any major surgical procedure or trauma, any current medical condition which could interfere with the evaluation of the subject and control subject is currently having sleep disorders.

Blood samples were obtained from patients admitted to Sleep Disorder Clinic of Department of Chest Diseases, Turgut Özal Medical Center (Malatya/Turkey) and diagnosed as OSAS by polysomnography. General characteristics of the study subjects were given in Table 1.

Sleep Parameters

Patients underwent polysomnography in the hospital using a digital polysomnographic monitor (Alice 6 LDx Diagnostic Sleep System, Philips, Germany). The sleep records were scored and evaluated by an experienced, registered polysomnologist following the American Academy for Sleep Medicine 2012 criteria (10). An apneic episode was defined as a ≥90% reduction of airflow lasting ≥10 seconds and hypopnea was characterized by a ≥30% reduction in breathing amplitude lasting ≥10 seconds and accompanied by an oxygen desaturation ≥ 3%. The sum of apnea and hypopnea events divided by the number of hours of sleep were defined as apnea hypopnea index (AHI). The patients were categorized according to severity of sleep apnea by AHI into three groups as mild sleep apnea: AHI 5-15/h; moderate sleep apnea: AHI: 16-29/h and severe sleep apnea: AHI ≥ 30/h.

Sample Preparation

Preparation of Erythrocyte Lysates and Lipid Extraction

Blood samples were taken into tubes containing EDTA and centrifuged at 1500 g for 10 min at 15°C. After the removal of the plasma and buffy coat, erythrocytes were diluted

with an equal volume of 0.9% NaCl and centrifuged at 900 g for 10 min. Having discarded the supernatant, lower fraction was taken to Eppendorf tubes containing 1 mg of BHT (2,6-di-tert-butyl-4-hydroxytoluene) and equal volume of saline was added and vortexed. Then the resultant erythrocyte suspensions were kept at -80°C until analyzed. The method of Bligh and Dyer (11) was used for the lipid extraction of 1mL of the erythrocyte lysates. The final extracts were evaporated under nitrogen and resuspended in 0.2 mL of chloroform and kept at 4°C until analyzed.

Hydrolysis of Phospholipids by Phospholipase C

To the extract from 1 mL of erythrocyte was added 2 mL of diethyl ether and vortexed for two min. Phospholipids in the extracts were hydrolyzed using *C. perfringens* phospholipase C (14 U/mL) in 0.5 mL of 50 mM potassium phosphate buffer, pH 7.0. Following the vortexing, the tubes were placed on a roller mixer and incubated for 3.5 h at room temperature before centrifugation at 1500 g for 7 min at 15°C. The upper diethyl ether phase was taken to another tube and evaporated to dryness under nitrogen.

Saponification of Acyl Groups

To evaporated extract of phospholipid hydrolysis was added 2.5 mL of 0.5 M KOH in methanol. Following vortexing, the tubes were heated in a boiling water bath for 10 min. The tubes were then allowed to cool and 4.5 mL of 6% glacial acetic acid in methanol were added. The contents were transferred to vial using 7 mL of chloroform. Samples were left stand overnight after adding 6 mL of water. The lower chloroform layer was taken to a tube. Then the upper phase extracted again with another 7 mL of chloroform. The combined chloroform extracts were evaporated to dryness, redissolved in 0.2 mL of chloroform and stored at 4°C.

Separation of O-Alkyl and O-Alkenyl Glycerolipids by TLC

TLC plates (Merck KGaA TLC Silica gel 60, 105721, Darmstadt, Germany) were used to separate and identify alkyl and alkenyl glycerolipids. 20x20cm TLC plates were activated at 110°C for one hour. 1-*O*-hexadecyl-sn-glycerol was used as control standard. The chromatography was conducted as described elsewhere (12). Chloroform/methanol/acetic acid (98:2:1; v/v/v) was used as mobile phase. After separation of alkyl and alkenyl glycerolipids, the plates were sprayed with an aqueous solution of 10% copper (II) sulphate in 8% phosphoric acid and charred at 180°C for 20 mins.

Densitometric Image Analysis of *O*-Alkyl and *O*-Alkenyl Spots on TLC Plates

Images of the TLC plates were loaded in file format of TIFF and the spots were located manually on the images. After background correction, the spots were densitometrically analyzed and the data were converted to raw volumes by the SYNGENE GeneTools quantification software (GeneTools software, version 4.03.05, Syngene, Cambridge, UK). The densitometric raw volumes determined was used as a measure of spot signal intensity in arbitrary units (a.u.).

Statistical Analysis

Analysis of covariance (ANCOVA) was used to perform comparisons based on the alkyl/alkenyl ratio whilst controlling for covariates. Age and body mass index (BMI) were considered as covariates and gender was considered as a random factor. The group to be compared was taken as a fixed factor in ANCOVA. For the other independent group comparisons, age and BMI were always considered as covariate and gender considered as random factor where appropriate in ANCOVA. In tables only the significance of the interested group variable was presented as a result of ANCOVA. Basic characteristics of the groups based on continuous variables were compared by independent samples t test. For categorical variables continuity-corrected chi-square was used and distribution of these data was represented by count and percentage. In all analysis two-tailed significance value was considered to be 0.05. IBM SPSS Statistics for Windows version 22.0 (NY, USA) was used for analyses.

RESULTS

Comparison of Subject Characteristics for Control versus Patients with OSA Group

30 patients with obstructive sleep apnea (OSA) diagnosed by overnight polysomnography and 30 control subjects were included in the study. Comparison of gender, age, BMI, medication, cigarette smoking and AHI values (where applicable) characteristics of both control and patients with OSA groups were depicted in Table 1. Some of the patients in OSA group suffered from chronic diseases such as hypertension (n=7), diabetes (n=7), coronary heart disease (n=1), thyroid disease (n=4) and hypertension + diabetes mellitus (n=4) and as a result they were taking some medications. Average age of OSA group was found to be 10 years higher compared to that of control group. BMI of OSA group was also significantly higher (8 kg/m²) compared to average control values. Of the patients, 11 and 18 were diagnosed as moderate and severe OSA. Only one of the patient's AHI indicated mild OSA.

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Table 1. Basic Characteristics of Study Subjects						
		Control Group		Patient Group		
		n	%	n	%	p
Gender*	Female	18	60.00	8	26.66	0.019
	Male	12	40.00	22	73.33	
Smoking Status*	Current	10	33.33	9	30.00	=1.000
	Never	20	66.66	21	70.00	
Medication*	User	-	0.00	15	50.00	<0.001
	Nonuser	30	100.00	15	50.00	
Age (Mean±SD)**		30	36.20±7	30	49.70 ± 7.8	<0.001
Body Mass Index (Mean±SD)**		30	24.71± 3.44	30	32.38 ± 6.05	<0.001
Apnea-HypopneaIndex (Mean±SD)		-	-	30	42.16±20.58	-
*Continuity corrected chi-square **Independent samples t test						

Table 2. The Impact of OSA on Age and BMI Adjusted Erythrocyte Alkyl/Alkenyl Ratios of Subgroups			
	Sub-group	Mean±SD	Test Statistics and p Values*
Total	Control (n=30)	6.92±3.91	F_{group} = 2.380
	Patient (n=30)	6.24±3.46	p_{group} = 0.157
Female	Control (n=21)	7.05±4.29	F_{group} = 1.273
	Patient (n=8)	6.36±4.81	p_{group} = 0.270
Male	Control (n=9)	6.60±3.04	F_{group} = 0.209
	Patient (n=22)	6.20±2.97	p_{group} = 0.651
Control	Female (n=21)	7.05±4.29	F_{gender} = 0.002
	Male (n=9)	6.60±3.04	p_{gender} = 0.968
Patient	Female (n=8)	6.36±4.81	F_{gender} = 0.009
	Male (n=22)	6.20±2.97	p_{gender} = 0.925
Control	Never smoked (n=20)	7.17±4.41	$F_{smoking\ status}$ = 0.013
	Current smoker (n=10)	6.41±2.77	$p_{smoking\ status}$ = 0.934
Patient	Never smoked (n=21)	6.75±3.80	$F_{smoking\ status}$ = 1.232
	Current smoker (n=9)	5.06±2.26	$p_{smoking\ status}$ = 0.350
Never Smoked	Control (n=20)	7.17±4.41	F_{group} = 0.003
	Patient (n=21)	6.75±3.80	p_{group} = 0.959
Current Smoker	Control (n=10)	6.41±2.77	F_{group} = 0.974
	Patient (n=9)	5.06±2.26	p_{group} = 0.493
Patient	AHI<30 (n=12)	6.55±3.97	F_{AHI} = 3.585
	AHI≥30 (n=18)	6.04±3.18	p_{AHI} = 0.251
Patient	No medication (n=15)	5.80±3.07	$F_{medication}$ = 2.204
	Medication user (n=15)	6.68±3.87	$p_{medication}$ = 0.522
*ANCOVA			

O-Alkyl/O-Alkenyl Glycerolipid Ratios in Erythrocyte Lysates of Control and OSA Group

Separation of alkyl/alkenyl glycerol bands of an erythrocyte lysate sample on the TLC plate can be seen in Fig.1. Analysis of covariance (ANCOVA) was used to perform comparisions between alkyl/alkenyl ratios of control and OSA group whilst controlling for covariates, age and BMI. Gender was considered as a random factor. The impact of OSA on age and BMI adjusted erythrocyte alkyl/alkenyl ratios in erythrocyte lysates of subgroups were shown in Table 2.OSA group had lower alkyl/alkenyl glycerolipid ratio compared to that of the control group albeit not significantly. The alteration in the ratio could be the result of either decreased level of alkyl glycerolipid or increased level of alkenyl glycerolipids or both. Similarly, lower alkyl/alkenyl gliserolipid ratios in women of sleep disorder group compared to that in women of control group is discernable, albeit insignificant. The same tendency could be observed between men of control and sleep disorder group. Interestingly, sleep disorder patients with AHI ≥ 30 had lower alkyl/alkenyl ratio than those with AHI<30. Moreover, cigarette smoking also appears to influence similarly the ratio either between smokers and non-smokers of sleep disorder patients or between smokers of control and sleep disorder patients, i.e. cigarette smoking appears to lower the ratio possibly in addition to the lowering effect of sleep disorder observed. Although no statistically significant correlation was found between any of the groups in the preceeding data, nevertheless they all point in the same direction.

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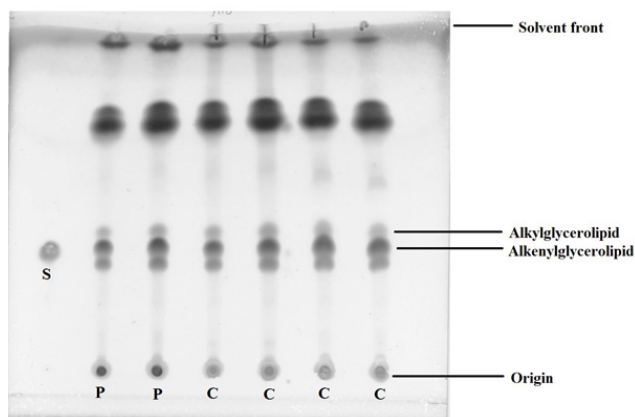
Figure 1. Chromatogram of Alkyl- and Alkenyl Glycerolipids of Eryhtrocyte Lysates
Phospholipids in erythrocyte lysates were hydrolyzed by phospholipase C and the acyl groups were saponified. The lipid extract was separated by TLC using chloroform/methanol/aceticacid (98:2:1; v/v/v) as mobile phase. After separation of alkyl and alkenyl glycerolipids, the plates were sprayed with an aqueous solution of 10% copper (II) sulphate and charred at 180 °C. Photometric image analyses were performed on the lipid spots of alkyl- and alkenylglycerolipids on TLC plates and the ratios were determined. S: Alkylglycerolipid standard (1-O-hexadecyl-sn-glycerol), C: Control, P: Patient.

DISCUSSION

The prevalence of OSA in the general adult population (at ≥ 15 events/h AHI) ranges from 6% to 17% which mounts to 49% in the advanced ages. The OSA prevalence is also greater in obese subjects (13). As the obesity epidemic continues to rise, the prevalence of OSA will likely to increase. Cardiovascular, neurocognitive and metabolic outcomes of OSA can adversely affect patients' health and quality of life. Epidemiologic studies suggest that OSA is under-diagnosed (14). Therefore appropriate testing is of importance. In the current work, alky /alkenyl glycerolipid ratios in erythrocyte lysates of patients with sleep apnea associated sleep disorders were compared to that of controls in an attemp to envisage any effect of OSA and to evaluate possible differences.

Mammalian erythrocytes contain both alkyl glyceryl ether and alk-1-enyl glyceryl ether (15). Plasmalogens constitute 15-20% of total phospholipids in cell membranes (including human erythrocytes), with ≥50% of glycerophosphoethanolamines in brain, heart, neutrophils and eosinophils (16). In our work, the alkyl/alkenyl ratio in control group was found to vary between 5.25-6.05 being higher compared to that have been reported in the literature. In human serum (≥40 years old), alkyl/alkenyl choline ratio (µM) was approx. 0.71-0.74, whereas alkyl/alkenyl

ethanolamine ratio was 0.07-0.09 (deduced with calculation from the resuts) (17). In human erythrocytes however, alkyl/alkenyl ratio in choline glycerophospholipid was 0.60/0 whereas in ethanolamine glycerophospholipid was 0.60/9.20=0.07 (18). In Connor et al work, average alkylacyl/alkenylacyl ratio was found to be 1.19 in choline glycerophospholipids and 0.96 in ethanolamine glycerophospholipids (value deduced by calculation from the relevant results) (19). The difference between our results and the others' can be attributed to the fact that we measured alkyl/alkenyl glycerolipids as whole whereas others analyzed individual choline and ethanolamine alkyl- and alkenylglycerophospholipids separately.Besides differences in the analysis methods used could also have contributed to the disparities.The techniques used range from LC-MS/MS (17), lipid phosphorus analysis following TLC separation (18) to HPLC analyses (19).Whereas we used densitometric image analysis of lipid spots on TLC plates. Additionally, the extent to which alkyl- and alkenylglycerolipids react with visualization reagent (copper II sulphate) may not be identical.

One aspect of sleep apnea is sleep restriction which is associated with circadian rhythm disturbances (20), whereas the other aspect is the hypoxia stress to which cells expose. Both sleep restriction and hypoxia have been reported to influence tissue lipid/phospholipid compositions including plasmalogens. Lipid peroxidation of erythrocytes due to hypoxia can influence erythrocyte membrane plasmalogen content. Since vinyl ether bond of cellular plasmalogens are highly susceptible to oxidation (21), high ROS levels and oxidative stress were found to be related to the decreased erythrocyte plasmalogen levels in Alzheimer's disease (9). Hypoxic stress was reported to cause an increase in plasmalogen content of red blood cells. (22). Because of OSA, increase in erythropoiesisinduced by hypoxia (23) can also possibly alter erythrocyte membrane lipid compositions The most altered plasma lipids as a function of sleep restriction are various glycerophospholipids including plasmalogens. Researchers observed increased plasma levels of plasmalogens after 5 days sleep restriction in both humans and rats. Metabolite changes in humans points out peroxisome involvement in sleep restriction. Across the both species, various phospholipids were the most elevated as a function of sleep restriction (4). On the contrary, Chua et al reported that plasma choline plasmalogen levels decreased in sleep deprivation (5). However Davies et al also found that 13 glycerophospholipids exhibited significantly increased levels in humans during sleep deprivation (3).

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As the preceeding data points out, various factors related to sleep apnea can implement a change in membrane lipid compositions. However in our work, comparisons of alkyl/alkenyl glycerolipid ratios in erythrocyte lysates between control and OSA group produced no significant differences. Some of the characteristics of our study subjects including age, gender, smoking and some diseases were found by other workers to alter plasmalogen content. Plasmalogen in human serum decreases with aging (24). On the other hand smoking is associated with plasmalogen deficiency in humans (25). Additionally, RBC plasmalogen content was observed to be increased in coronary heart disease (22) whereas decreased in diabetic patients (26). On the other hand, no sex-specific differences in human RBC plasmalogen levels or composition were observed (27). Nevertheless, in our work, the impact of OSA on age and BMI adjusted erythrocyte alkyl/alkenyl ratios in erythrocyte lysates produced no statistically significant differences between subgroups.

The findings of this study have to be seen in light of some limitations. BMI and age of control subjects do not match well those of patients with OSA. Since the prevalence in the general adult population is high in the advanced ages and obese men and women, we were unable to find control subjects matched with OSA patients in terms of BMI and age because of time constraint. This might have caused wide variations in alkyl/alkenyl ratios in erythrocytes of subjects. Besides, sensitivity of TLC method used in the current work is not comparable to the modern analytical techniques. Todays, lipidomic analyses by LC-MS/MS offers high sensitivity for detection of low abundance plasmalogen molecular species in human serum which enables measurement of nanomolar concantrations (28). Since dietary plasmalogens were reported to cause increases in relative plasmalogen composition of erythrocyte membranes (29) consumption of foods by subjects with varying plasmalogen level could be another factor causing high variation.

We did not find any significant difference between sleep apnea patients and controls in terms of alkyl/alkenyl ratios in erythrocytes, probably due to high variations between individuals. However, the current results warrant reinvestigation of erythrocyte alkyl-/ alkenyl-glycerolipid ratios in subjects with sleep apnea since we believe that individual variations in lipid parameters could have obscured the possible link between them. In order to overcome this, we suggest that the alkyl/alkenyl glycerol ratios of erythrocytes in samples of the same indiviual taken before and after the treatment of apnea (CPAP therapy) should be compared in order to better understand the potential of this ratio as diagnostic tool.

DECLARATIONS

Ethics

All the research procedures were conducted according to guidelines set by İnönü University Malatya Clinical Research Ethical Committee (protocol number: 2016/198).

Conflict of Interest

The authors declares no conflict of interest.

Authors' Contributions

Emine Koç collected the data, contributed the data analysis, performed the analyses, contributed to the manuscript writing. Hilal Ermiş collected the polysomnographic data. Gözde Harika Gözükara Bağ conducted statistical analyses. Muhammed Dündar performed the densitometric image analyses. Tayfun Güldür established the hypothesis, designed the experiments and contributed to the data analyses and the manuscript writing.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   General and Internal Medicine / Genel ve Dahili Tıp

Effects of Anemia on Clinical Outcomes in Hospitalized Patients with COVID-19 Pneumonia

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ABSTRACT

Objective: We aimed to examine the role of anemia on clinical outcomes including intensive care unit (ICU) admission and mechanical ventilation (MV) in coronavirus disease 2019 (COVID-19) patients.

Materials and methods: Totally 175 hospitalized COVID-19 patients were retrospectively included. Patients with a hemoglobin level of <12 g/dL in women and <13 g/dL in men constituted the anemic group, while COVID-19 patients with normal hemoglobin levels constituted the non-anemic group. A logistic regression analysis was performed to investigate the role of anemia and serum ferritin value for prediction of ICU and MV requirement.

Results: Of patients, 46 (45.7%, 21 men) had anemia and 129 (68.2%, 88 men) had normal hemoglobin levels. The ICU requirement and MV rates were significantly higher in anemic group compared to non-anemic group (30.4% vs. 15.5%, respectively; p=0.028 and 23.9% vs. 10.9%, respectively; p=0.030). Median length of hospital and ICU stay was longer in patients with anemia (10.5 days vs. 8 days, respectively; p=0.047 and 0 days vs. 0 days, respectively; p=0.027). Anemia and ferritin were significant risk factors for ICU admission in univariate model and multivariate model [OR: 2.384 (95% CI: 1.084-5.246), p=0.031] vs. [OR: 2.738 (95% CI: 1.130-6.635), p=0.026) and [OR: 5.058 (95% CI: 1.968-12.998), p=0.001] vs. [OR: 4.218 (95% CI: 1.521-11.697), p=0.006). Anemia was also a risk factor for MV [OR: 2.582 (95% CI: 1.075-6.197), p=0.034].

Conclusion: Requirement for therapy in ICU and MV were high among anemic COVID-19 patients. Anemia is also associated with prolonged length of stay in hospital and ICU.

Keywords: Coronavirus disease 2019 (COVID-19); anemia; ferritin; intensive care unit; mechanical ventilation

COVID-19 Pnömonisi Nedeni ile Yatarak Tedavi Gören Hastalarda Aneminin Klinik Sonuçlara Etkisi

ÖZET

Amaç: COVID-19 hastalarında aneminin yoğun bakım ünitesine yatış ve mekanik ventilasyon gibi klnik sonuçlara etkilerini incelemeyi amaçladık.

Materyal ve metodlar: Toplam 175 yatarak tedavi gören COVID-19 hastası retrospektif olarak çalışmaya alındı. Kadınlarda hemoglobin düzeyi <12 g/dL ve erkeklerde <13 g/dL olan hastalar anemi grubunu oluştururken, normal hemoglobin düzeyi olan hastalar anemik olmayan grubu oluşturdu. Anemi ve ferritin seviyesinin yoğun bakım ve mekanik ventilasyon ihtiyacını öngörmede rolü lojistik regresyon analizi ile incelendi.

Bulgular: Hastalardan 46'sı (%45.7, 21 erkek) anemik ve 129'u (%68.2, 88 erkek) normal hemoglobin düzeylerine sahipti. Yoğun bakım ihtiyacı ve mekanik ventilasyon hızı anemik hastalarda anemik olmayanlara göre anlamlı oranda yüksekti (%30.4 vs. %15.5, sırasıyla; p=0.028 ve %23.9 vs. %10.9, sırasıyla; p=0.030). Medyan hastanede ve yoğun bakımda kalış süreleri anemik hastalarda daha uzundu (10.5 gün vs. 8 gün; p=0.047). Anemi ve ferritin düzeyi tek değişkenli ve çok değişkenli analizlerde yoğun bakıma yatış için belirgin risk faktörü olarak saptandı [OR: 2.384 (%95 CI: 1.084-5.246), p=0.031] vs. [OR: 2.738 (%95 CI: 1.130-6.635), p=0.026) ve[OR: 5.058 (%95 CI: 1.968-12.998), p=0.001] vs. [OR: 4.218 (%95 CI: 1.521-11.697), p=0.006]. Anemi mekanik ventilasyon için de risk faktörü olarak saptandı [OR: 2.582 (%95 CI: 1.075-6.197), p=0.034].

Sonuçlar: Anemik Covid-19 hastalarında yoğun bakım ve mekanik ventilasyon ihtiyacı yüksekti Anemi aynı zamanda hastane ve yoğun bakımda uzamış kalış süreleri ile ilişkili bulundu.

Anahtar sözcükler: COVID-19 (koronavirüs hastalığı 2019); anemi; ferritin; yoğun bakım ünitesi; mekanik ventilasyon

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Novel coronavirus 2019 (COVID-19) outbreak, which first emerged in Wuhan, Hubei province of China in December 2019, continues as a serious pandemic affecting millions of individuals around the world. The disease severity varies among individuals from mild asymptomatic disease to severe pneumonia. COVID-19 pneumonia, which can involve multiple lung segments, may cause mild, moderate or severe disease (1). Although most infections have a mild clinical course, up to 20% of infected patients need to be hospitalized mainly for pneumonia, and some of these patients may need therapy in an intensive care unit (ICU) and may require mechanical ventilation (MV) (2,3). It has been reported that, in severe cases, dyspnea and hypoxemia are often observed, and a group of patients develop septic shock and acute respiratory distress syndrome (ARDS) (4). Approximately 5 to 8% of the total infected population and 25% of all hospitalized patients need hospitalization in the ICU setting (5). COVID-19 infection may also lead to multiple organ dysfunction syndrome, resulting in increased inflammation, cytokine storm, hypoxia, and thrombosis (6). However, the underlying pathophysiology affecting clinical endpoints has not been completely elucidated, yet. Theoretically, anemia may play an important role in the development of multiple organ failure by reducing oxygen transport to tissues (7).

Anemia is a common health problem affecting approximately 2 billion individuals worldwide (8). It has been associated with many critical illnesses (9). It increases mortality and morbidity in many diseases such as heart failure, chronic obstructive pulmonary disease, and myocardial infarction (10-12). A higher rate of mortality has been observed in anemic patients with community-acquired pneumonia (13).

Serum ferritin is one of the biomarkers of iron deficiency anemia. Ferritin level reflects iron or iron accumulation stored in liver tissue. Therefore, the level of ferritin is low in iron deficiency anemia (14). On the other hand, a high ferritin level may indicate a chronic inflammatory process or the presence of infection (15). Ferritin is an acute phase protein which can be also assessed in various inflammatory diseases. Ferritin levels of up to 10,000 ng/mL can be seen in macrophage activation syndrome (16). In COVID-19, low hemoglobin levels may be one of the reasons of failed supply of the increased oxygen demand at peripheral tissues due to hypermetabolic conditions that develop during infection.

In the present study, we aimed to examine the relationship between the initial hemoglobin level during hospitalization and duration of hospital stay, ICU and MV requirement and duration of ICU in patients with COVID-19 pneumonia. In addition, we investigated the role of the serum ferritin in the clinical course of COVID-19 disease and to identify whether anemia was a possible predictor of ICU and MV for COVID-19 disease.

MATERIALS AND METHODS

This multi-center, retrospective study was conducted between march 2020 and may 2020. The study protocol was approved by the institutional Ethics Committee (No: 2021-05/26, Date: 03/10/2021). The study was also approved by the central government health authority with the approval number of 2021-03-03T00_03_17. The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from all patients included in the study.

A total of 175 adult (≥18 years) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) cases with a confirmed diagnosis by real-time polymerase chain reaction (RT-PCR) who had ground glass appearance and/or consolidation compatible with COVID-19 pneumonia on thoracic computed tomography (CT) were included in the study. Patients with missing medical data, having pregnancy, and age under 18 years were excluded. Clinical characteristics, symptoms and laboratory parameters of patients were recorded on the electronic patient data sheet. Clinical outcomes were retrieved from the hospital database and recorded. The length of hospitalization, therapy interval at ICU, requirement for MV, and clinical events were noted.

Blood samples were collected within 4 h after admission to perform routine laboratory tests including complete blood count, coagulation tests, and biochemical assays. Blood counts were performed using the Sysmex™ Xn 1800i (Sysmex Co., Kobe, Japan) system. Inter- and intra-day variability coefficients were calculated as 3.5% and 4.1%, respectively. All measurements were carried out within 2 h after blood sampling.

Patients with a hemoglobin level of <12 g/dL in women and <13 g/dL in men were considered as anemic and consisted the anemic group. The COVID-19 patients with normal hemoglobin levels consisted the non-anemic group. Normal ferritin values were accepted between 22 ng/dL

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and 322 ng/dL and normal D-dimer values were accepted below 0.5 ug/mL in our laboratory.

In our study, the presence of tachypnea (respiratory rate >30/min), progressive dyspnea and increased work of breathing, peripheral oxygen saturation (SpO$_2$) <90% without response to oxygen up to 12 L/min with reservoir, lactate levels of >2 mmol/L, and systolic blood pressure below 80 mmHg were the indications for ICU admission. Despite high-flow oxygen therapy and non-invasive MV therapy, blood gas analysis oxygen saturation (SaO$_2$) <90%, pH <7.3, and carbon dioxide (CO$_2$) >50 mmHg, increased respiratory work, worsening mental state, hemodynamic instability, or multiple organ failure were the indications for MV.

Both study groups were compared in terms of demographic features, ICU and MV requirements, and duration of hospitalization.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 statistical software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the distributions of continuous variables were normal or not. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) and interquartile range (IQR) or number and frequency, where applicable. The Student t-test and Mann-Whitney U tests were used to compare the normally and non-normally distributed numerical variables between the study groups. Categorical variables were compared using the chi-square (χ^2) test. Since the ferritin value was non-normally distributed, log-transformation was performed. Normally distributed log-transformed ferritin values were included in the logistic regression analysis. Univariate and multivariate binary logistic regression analysis with the enter mode were carried out to investigate the predictive value of anemia and serum ferritin value (log-transformed) for ICU and MV requirements. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients 46 had anemia and 129 had normal hemoglobin levels. The COVID-19 patients in the anemic group were older than the patients in non-anemic group (55.0±13.5 years vs. 49.0±13.45 years, respectively; p=0.011). There was also a statistically significant difference regarding male sex between the anemic and non-anemic patient groups [(45.7% (n=21) vs. 68.2% (n=88), respectively; p= 0.007].

In our study, ferritin values were pathologically high in both groups of patients hospitalized due to COVID-19. However, the median ferritin values in both groups were measured as 324 ng/dL (range, 6 to 3700, IQR=464) in the anemic group and 318 ng/dL (range, 0 to 2727, IQR=366) in the non-anemic group, respectively, indicating no statistically significant difference between the groups (p=0.941).

The median D-dimer values were measured as 0.65 ug/mL (range, 0.14 to 8300, IQR=0.9) in the anemic group and 0.58 ug/dL (range, 0.12 to 4.91, IQR=0.44) in the non-anemic group and D-dimer values were also pathologically high in both study groups. There was no statistically significant difference in the D-dimer values between the groups (p=0.231).

The prevalence of hypertension, diabetes mellitus, heart failure, smoking status were similar between the groups. However, coronary artery disease was more common in the anemic group (p=0.036). Baseline demographic and clinical characteristics and laboratory parameters are shown in Table 1.

The median total length of hospitalization was longer in the anemic group, compared to the non-anemic group, indicating a statistically significant difference (10.5 days (range, 4 to 32) vs. 8 days (range, 3 to 73), respectively; p=0.047). Also, the rate of the patients requiring hospitalization in the ICU was significantly higher in the anemic group (30.4% vs. 15.5%, respectively; p=0.028) (Figure 1). The median length of stay in the ICU was also longer in the anemic group, indicating a statistically significant difference (0 days (range, 0 to 22), IQR=6.5 vs. 0 days (range, 0 to 69), IQR=0, respectively; p=0.027).

In our study, two patients in the anemic COVID-19 group and one patient in the non-anemic COVID-19 group died in the ICU setting due to respiratory distress syndrome and multiple organ failure. Comparison of clinical outcomes among COVID-19 patients with and without anemia, including the need for ICU admission and the need for MV, as well as length of stay in the hospital and ICU, are presented in Table 2.

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Table 1. Baseline demographics, clinical characteristics and laboratory parameters of patients			
	Anemic group (n=46)	**Non-anemic group (n=129)**	**P value**
Age (years)	55.0 ± 13.5	49.0 ± 13.5	**0,011†**
Sex (male)	21 (45.7%)	88 (68.2%)	**0,007#**
Diabetes mellitus	4 (8.7%)	14 (10.9%)	0,679#
Hypertension	14 (30.4%)	39 (30.2%)	0,980#
Coronary artery disease	7 (15.2%)	7 (5.4%)	**0.036#**
Heart failure	1 (2.2%)	0 (0 %)	0.263*
Cigarette smoking	11 (23.9%)	33 (25.6%)	0,823#
Hemoglobin (g/dL)	11.7±0.9	14.2±1.1	**<0.001†**
Ferritin (ng/dl)	324 (6-3700) IQR = 464	318 (0-2727) IQR = 366	0.941§
D-dimer (ug/ml)	0.65 (0.14-8300) IQR = 0.90	0.58 (0.12-4.91) IQR = 0.44	0.231§
MCV	83±4	86±4	0.653
MCHC	33.5±1.2	34.6±1.3	0.467
Creatinine	1.05±0.05	1.03±0.04	0.726

Data are shown as mean ± standard deviation (SD), median (min-max, IQR) and n (%), unless otherwise stated. †Student t-test, §Mann-Whitney U test, #chi-square test, *Fisher exact test. IQR: interquartile range, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration.

Figure 1. Distribution of study groups according to ICU admission

Table 2. Comparison of clinical outcomes			
	Anemic group (n=46)	**Non-anemic group (n=129)**	**P value**
Hospitalization (days)	10.5 (4-32) IQR=9	8 (3-73) IQR=8	**0,047§**
ICU admission	14 (30.4%)	20 (15.5%)	**0.028#**
MV	11 (23.9%)	14 (10.9%)	**0.030#**
ICU duration (days)	0 (0 – 22) IQR=6.5	0 (0 – 69) IQR=0	**0.027§**

Data are shown as median (min-max, IQR) and n (%), unless otherwise stated. §Mann -Whitney U test, #chi-square test, IQR: interquartile range, ICU: Intensive Care Unit, MV: Mechanical Ventilation.

Figure 2. Distribution of study groups according to MV requirement

In the logistic regression analysis, anemia was found to be a statistically significant risk factor in the univariate model [OR: 2.384 (95% CI: 1.084-5.246), p=0.031] and multivariate model (age- and sex-adjusted) [OR: 2.738 (95% CI: 1.130-6.635), p=0.026] for ICU admission. Log-transformed ferritin value in both univariate [OR: 5.058 (95% CI: 1.968-12.998), p=0.001] and multivariate models [OR: 4.218 (95% CI: 1.521-11.697), p=0.006] was also found to be a statistically significant risk factor for ICU (Table 3).

The patients with anemia did not respond well to high-flow oxygen therapy and non-invasive MV support with bilevel positive airway pressure (BiPAP). COVID-19 patients with anemia needed more frequently endotracheal intubation and MV therapy (23.9% vs. 10.9%, respectively; p=0.030) (Figure 2). Using the logistic regression analysis in the univariate model, anemia was found to be a statistically significant risk factor for MV requirement [OR: 2.582 (95% CI: 1.075-6.197), p=0.034]. However, in the multivariate model, anemia was not found to be a statistically significant risk factor MV requirement [OR: 2.322 (95% CI: 0.886-6.086), p=0.087]. Additionally, for the MV requirement, log-ferritin value was found to be a statistically significant risk factor in the univariate model [OR: 5.500 (95% CI: 1.871-16.165), p=0.002] and multivariate model [OR: 5.596 (95% CI: 1.738-18.011), p=0.004], respectively (Table 4).

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Table 3. Possible predictors for ICU admission

	Univariate model			Multivariate model			
	OR	95% CI		P value	OR	95% CI		P value
Age	1.025	0.997	1.054	0.079	1.014	0.982	1.048	0.381
Male sex	2.271	0.961	5.370	0.062	1.657	0.612	4.485	0.320
Anemia	2.384	1.084	5.246	**0.031**	2.738	1.130	6.635	**0.026**
Log ferritin	5.058	1.968	12.998	**0.001**	4.218	1.521	11.697	**0.006**

CI; Confidence Interval, OR; Odds Ratio, ferritin values are shown as log-transformed.

Table 4. Possible predictors for mechanical ventilation

	Univariate model			Multivariate model			
	OR	95% CI		P value	OR	95% CI		P value
Age	1.052	1.019	1.087	**0.002**	1.048	1.010	1.087	**0.013**
Male sex	1.340	0.543	3.303	0.525	0.892	0.308	2.586	0.834
Anemia	2.582	1.075	6.197	**0.034**	2.322	0.886	6.086	0.087
Log ferritin	5.500	1.871	16.165	**0.002**	5.596	1.738	18.011	**0.004**

CI; Confidence Interval, OR; Odds Ratio, ferritin values are shown as log-transformed.

DISCUSSION

The present study clearly showed that COVID-19 disease was clinically progressed more severely in patients with low hemoglobin levels during hospital admission. These results also indicated that almost one-fourth of the COVID-19 patients with anemia experienced more severe hypoxia requiring therapy in the ICU setting which did not respond adequately to high-flow oxygen therapy and non-invasive MV support through BiPAP systems, thereby, leading to endotracheal intubation and MV.

Although lower hemoglobin levels have been reported in critical COVID-19 patients, the exact relationship between these two conditions has not been fully understood, yet (17). Until now, there are few studies examining the effect of anemia on the progression and outcomes of COVID-19. In a recent study including 67 COVID-19 patients in Singapore, patients followed in the ICU had lower hemoglobin levels, compared to those followed in the ward (18). Another study reported that anemia was associated with a severe inflammatory response and could be an independent risk factor for COVID-19 (19). However, there are no conclusive data yet indicating the impact of anemia on disease prognosis in COVID-19. To the best of our knowledge, there is a limited number of studies examining the relationship between pre-existing anemia and COVID-19 disease in the literature, as in our study (20).

Anemia potentially worsens the clinical situation in COVID-19 patients. It has been proposed that SARS-CoV-2 can interact with hemoglobin molecules on the erythrocyte via angiotensin-converting enzyme 2 (ACE2), cluster of differentiation 147 (CD147), and cluster of differentiation 26 (CD26) receptors. This virus-hemoglobin interaction has been shown to result in a viral attack to the heme circle in the beta-1 chain of hemoglobin that can cause hemolysis (21). Furthermore, SARS-CoV-2 can mimic the effect of hepcidin, which increases circulating and tissue ferritin while causing serum iron deficiency, and decreases hemoglobin levels (22). Hepcidin is a hormone which regulates the iron metabolism, modifying iron balance by reducing iron in the organism and preventing duodenal iron absorption and macrophage iron release (23). Also, hepcidin is an acute phase reactant and its synthesis from the liver increases in the presence of inflammation. Hemoglobin concentration is one of the main determinants of the oxygen carrying capacity of the blood. We believe that, as a result of the increased metabolic activities that develop in the course of infectious diseases, the increased oxygen demand of peripheral tissues cannot be supplied sufficiently in patients with low hemoglobin levels. Therefore, low hemoglobin concentration in anemic patients may cause inadequate delivery of oxygen to organs, resulting in various organ dysfunctions. The damage in respiratory system contributes to the development of hypoxia at tissue level (24). As a result of the increased inflammatory and thrombotic mechanisms, multiple organ dysfunction and failure cause worse clinical outcomes in COVID-19.

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In addition to showing iron stores in iron deficiency anemia, ferritin also plays a role as an acute phase reactant in infectious diseases. Ferritin has been shown in previous studies as a pro-inflammatory factor in cytokine storm and a predictor of poor outcomes in COVID-19 patients (25). The increased oxidative stress and lipo-peroxidation may also accelerate inflammatory response, leading to the increased responsiveness of the immune system resulting in the "cytokine storm" phenomenon (26). The increased ferritin levels may lead to a phenomenon so called "ferroptosis", which can be defined as an iron-dependent cell death form.

Similar to our study results, in a systematic review and meta-analysis by Cheng et al. (25), high ferritin levels in COVID-19 were associated with the ICU transfer under intensive supportive care, including MV. Furthermore, in our study, ferritin value increased the need for ICU and MV, regardless of age and sex in the multivariate analysis.

In recent studies evaluating COVID-19 pneumonia risk factors, advanced age and male sex were associated with higher in-hospital mortality rates and usually worse in-hospital outcomes in hospitalized COVID-19 patients (27-30). In addition, male sex was independently associated with the need for ICU (31). In our study, the mean age of anemic patients was higher and the number of male patients was lower in the anemic group. However, in the multivariate analysis, we observed that anemia increased the need for intensive care regardless of age, sex, and ferritin value. While anemia significantly increased the need for MV in the univariate analysis, multivariate analysis revealed no significant correlation of the age, sex, and ferritin values with the need for MV. This can be attributed to the low sample size and the effect of confounding risk factors. Correlations between other independent factors and anemia may have affected the results.

Recently, the number of COVID-19 patients has been increasing worldwide. As a result, the number of critically ill patients requiring intensive care has dramatically increased. Early recognition of severe forms and timely triage of patients is of utmost importance. While the clinical condition of the patients, SpO_2 levels and comorbidities are the main determinants of the need for ICU admission, some laboratory parameters may also facilitate the assessment of the severity of the disease. We believe that anemic patients should be recommended to take additional precautions to minimize their risk of exposure to the virus. In addition, anemic patients with suspected COVID-19 should be followed more closely to detect signs of disease progression. In our opinion, anemia diagnosed at the first admission to the hospital in COVID-19 patients may be an important factor in future risk classification models to predict the progression of the disease.

The main limitations of our study include that the mortality status in the study population was unable to be evaluated. In future large-scale studies, the relationship of anemia not only with ICU and MV, but also with mortality should be examined. In addition, different models can be created for male and female patient groups.

In conclusion, anemic COVID-19 patients need more frequent ICU hospitalization and MV therapy. In addition, these patients have prolonged hospital and ICU stay. Anemic patients should be followed more closely in terms of disease progression. Consideration of anemia at the time of admission may be helpful in COVID-19 patient management and risk stratification.

DECLARATIONS

Conflict of Interests
The authors declare they have no conflict of interest.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Internal Medicine / İç Hastalıkları

COVID-19 in Geriatric Patients

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ABSTRACT

Objective: Considering the ongoing pneumonia epidemic associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), aging is a major risk factor alone for serious illness and death. In this study, we aimed to investigate the length of stay, hospital discharge status, and prognostic factors in geriatric patients with COVID-19.

Methods: Medical files of 199 patients over the age of 65 years, who were treated as inpatients due to the diagnosis of COVID-19, were reviewed retrospectively. Demographic characteristics, comorbid diseases, laboratory values, the length of stay, and hospital discharge status of eligible patients were evaluated.

Results: Of inpatients with COVID-19, the mean age was 75.01±7.86 years and 50.8% were men. In patients, who were transferred to ICU, C-reactive protein (CRP) and ferritin levels were higher compared to patients discharged to home and the monocyte/HDL ratio (MHR) was higher compared to nonsurvivors (p=0.037, p=0.003, p=0.023). Nonsurvivors had significantly higher white blood cell (WBC) counts and erythrocyte sedimentation rates (ESR) compared to patients discharged to home. Nonsurvivors had a significantly shorter length of hospital stay compared to patients, who were transferred to ICU.

Conclusion: Geriatric patients are susceptible to adverse clinical outcomes of COVID-19. We think that WBC, ESR, CRP, ferritin, and MHR levels may inform about poor prognosis and the potential discharge status in older adult patients with COVID-19 pneumonia. Gaining insight into poor prognostic factors in older adult patients is essential to control COVID-19 and develop rapid treatment strategies in this age group.

Keywords: Geriatrics, COVID 19, İnflammation.

Geriatrik Hastalarda COVİD-19

ÖZET

Amaç: Şiddetli akut solunum yolu koronavirüsü 2 (SARS-CoV-2) ile ilişkili devam eden pnömoni salgınında yaşlanmanın kendisi, ciddi hastalık ve ölüm için önemli bir risk faktörüdür. Bu çalışmada COVID-19'lu yaşlı hastaların yatış sürelerini, çıkış durumlarını ve prognostik faktörleri araştırmayı planladık.

Hastalar ve Yöntem: COVID-19 tanısı ile takip edilen 65 yaş üstü 199 hastanın dosyası retrospektif olarak tarandı. Çalışmaya alınan hastaların demografik özellikleri, komorbid hastalıkları, labaratuvar değerleri, yatış süreleri ve çıkış durumları değerlendirildi.

Bulgular: COVID-19 tanısı ile yatan hastaların yaş ortalaması 75,01±7,86 'ıydı ve %50,8'i erkekti. Yoğun bakıma sevk edilen hastaların C-reactive protein (CRP) ve ferritin düzeyleri eve taburcu olanlardan, monosit/HDL oranı (MHR) exitus olanlardan anlamlı derecede daha yüksekti (p=0.037, p=0.003, p=0.023). Exitus olan hastaların beyaz kan hücresi (WBC) ve erythrocyte sedimentation rate (ESR) düzeyleri eve taburcu olan hastalardan anlamlı derecede daha yüksekti ve yatış süreleri yoğun bakıma sevk edilen hastalardan anlamlı derecede kısa idi (p<0.05).

Sonuç: Yaşlı hastalar, COVID-19 enfeksiyonunda olumsuz klinik sonuçlara duyarlıdır, değerlendirme ve tedavileri zordur. COVID-19 pnömonili yaşlı hastalarda WBC, ESR CRP, ferritin ve MHR gibi parametrelerin kötü prognozu gösterebileceğini ve bunların hastaların çıkış durumuyla ilişkilendirilebileceğini düşünüyoruz. Yaşlı hastalarda bu kötü prognostik faktörleri anlamak COVID-19 enfeksiyonunu kontrol etmek ve hızlı tedavi stratejileri geliştirmek için gereklidir.

Anahtar Kelimeler: Geriatri, COVID 19, İnflamasyon

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The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in China caused the pandemic to date, resulting in uncontrollable disease outbreaks, significant death rates, and long-term disability (1). Although the pathophysiology of the disease is complex and not completely understood, it is suggested that SARS-CoV-2, similar to SARS-CoV-1, primarily targets pulmonary epithelial cells and induces reductions in the production of proinflammatory cytokines and impairs T-cell response (2).

Any individual from any age group is at risk of contracting the SARS-CoV-2 infection and developing severe disease. SARS-CoV-2 infection, also known as coronavirus disease-19 (COVID-19) can be asymptomatic or may manifest itself in many clinical pictures ranging from a mild flu-like disease to more severe manifestations with life-threatening complications. SARS-CoV-2 not only acts on the respiratory airways and causes pneumonia but may affect the gastrointestinal system (GIS), nervous system, or cardiovascular system as well (3). However, compared to younger individuals, geriatric patients are more susceptible to develop severe SARS-CoV-2 infection because of compromised immune reactions, comorbidities, and underlying disorders. Management of older adult patients with COVID-19 requires extra attention compared to younger patients (4).

Real-time reverse transcription-PCR (RT-PCR) continues to be used as the most common method to identify SARS-CoV-2 (5). In addition to the identification of SARS-CoV-2; routine hematological, biochemical, and chemical laboratory test parameters can be employed as markers to monitor the patient's condition or to detect potential clues reflecting the disease state (6,7). Lymphopenia, neutropenia, and high levels of plasma inflammatory markers were associated with disease severity and the risk of death in previous studies (8). In this study, we aimed to investigate the hematological and biochemical markers that might be associated with the length of hospital stay and discharge status of patients over 65 years of age, who were admitted to our inpatient unit due to the diagnosis of COVID-19.

MATERIAL AND METHOD

This retrospective study was approved by Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 17/05/2021, No:111/07). All procedures were carried out in compliance with the principles of the Declaration of Helsinki. Medical files of 199 patients over 65 years of age, who were treated in our hospital's inpatient care unit because of COVID-19 in the period between January 2020 and January 2021, were reviewed retrospectively. The diagnosis of COVID-19 was confirmed via RT-PCR tests in the oropharyngeal swab or sputum samples of the patients. Patients included in the study were evaluated for age, gender, levels of laboratory test parameters, the length of hospital stay, and discharge status. Comorbidities were categorized as hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and heart disease (HD). The length of stay was defined as the time from admission to death, to discharge to home, or to the transfer to the intensive care unit (ICU).

The neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the monocyte-to-HDL ratio (MHR) have been in use so far as inexpensive and easy-to-calculate parameters to evaluate systemic inflammation in clinical practice (9,10). It has been reported that NLR, PLR, and MHR values may guide the diagnosis and prognosis in many systemic diseases such as malignancies, chronic inflammatory diseases, acute myocardial infarction, renal artery stenosis, or diabetes mellitus (11,12). NLR is calculated by dividing the neutrophil count by the lymphocyte count. PLR is calculated by dividing the platelet count by the lymphocyte count. MHR is calculated by dividing the monocyte count by the measured value of high-density lipoprotein cholesterol (HDL). We examined NLR, PLR, and MHR values in geriatric patients, who were admitted to our inpatient service because of the diagnosis of COVID-19 at the time of admission. The study population underwent blood tests after 12-hour fasting for the measurement of HDL Cholesterol, through enzymatic colorimetric assay.

Statistical Analysis

A total of 199 patients were included in the analysis. The statistical analyses were carried out using IBM SPSS Statistics-26 package software. The study data were summarized in frequencies (number, percentage) for categorical variables. Descriptive statistics (mean, standard deviation) were used to summarize numerical variables. The normality assumptions of the numerical variables were examined by the Kolmogorov Smirnov normality test. It was observed that the variables were normally distributed. Therefore, parametric statistical methods were used for further analysis.

Differences between two independent groups were examined by the independent samples t-test. Differences between more than two independent groups were

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analyzed by One-Way Analysis of Variance (ANOVA). When differences were identified between the groups based on the results of ANOVA, Tukey's multiple comparison test was used. The relationships between two independent numerical variables were interpreted by using Pearson's correlation coefficient. Relationships between two independent categorical variables were analyzed by the chi-square analysis. Statistical significance was interpreted at the 0.05 level for all statistical test results.

RESULTS

The mean age of patients, who were admitted to the inpatient unit due to the diagnosis of COVID-19, was 75.01±7.86 years. Of the patients; 49.2% were women and 50.8% were men. HT was present in 67.3% of the patients, DM in 35.7%, HD in 27.1%, and COPD was present in 15.6% of the patients. The mean length of hospital stay was 11.82±6.20 days. The discharge status of the patients was the discharge to home in 65.3%, transfer to ICU in 12.6%, and death in 22.1% (Table 1).

The length of hospital stay was statistically significantly different by the hospital discharge status of the patients (p<0.05). The length of hospital stay was significantly shorter in nonsurvivors and in patients, who were discharged to home compared to that of patients, who were transferred to ICU (p<0.001). There was a low-level but positive and statistically significant correlation between the length of stay and the WBC count (r=0.139) (Table 2).

WBC, C-reactive protein (CRP), ferritin, HDL, erythrocyte sedimentation rate (ESR), and MHR levels were statistically significantly different by the discharge status of patients (p<0.05). CRP and ferritin levels of the patients, who were transferred to ICU, were significantly higher than those of patients, who were discharged to home (p=0.037, p=0.003). MHR values of the patients, who were transferred to ICU, were significantly higher compared to those of nonsurvivors (p=0.023). HDL levels of nonsurvivors were significantly higher compared to those of patients, who were discharged to home or transferred to ICU (p<0.001). Nonsurvivors had significantly higher WBC and ESR levels than those of patients, who were discharged to home (0.002, 0.015) (Table 3).

Table 1. Demographic characteristics of patients (n=199)	
	n (%)
Gender	
Women	98 (49.2)
Men	101 (50.8)
Discharge Status	
Home	130 (65.3)
ICU	25 (12.6)
Death	44 (22.1)
HT	
Yes	134 (67.3)
No	65 (32.7)
DM	
Yes	71 (35.7)
No	128 (64.3)
COPD	
Yes	31 (15.6)
No	168 (84.4)
HD	
Yes	54(27.1)
No	145(72.9)
	Mean±S.D.
Age	75.01±7.86
Length of Hospital Stay	11.82±6.20
ICU: Intensive care unit, S.D.: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, HD: Heart disease	

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Table 2. Relationship between the length of stay and other variables			
	Length of Stay		
	Mean± S.D.	**Test**	**p**
Gender		t: -0.246	0.806
Women	11.71±4.99		
Men	11.93±7.21		
Discharge Status		F: 23.269	<0.001*
		Difference: 2-1,3	
1.Home	10.42±4.56		
2.ICU	18.76±7.69		
3.Death	12.02±6.89		
HT		t: -0.717	0.474
Yes	11.60±6.33		
No	12.28±5.94		
DM		t: 1.255	0.211
Yes	12.56±5.92		
No	11.41±6.33		
COPD		t: 0.770	0.442
Yes	12.61±6.68		
No	11.68±6.11		
HD		t: 1.275	0.204
Yes	12.74±7.44		
No	11.48±5.66		
		r	**p**
Age		-0.109	0.127
WBC (×103 µl)		0.139*	0.049
NEU (×103 µl)		0.038	0.592
LYM (×103 µl)		0.011	0.876
PLT (×103 µl)		0.032	0.652
MON (×103 µl)		0.027	0.71
D-Dimer (µg/ml)		0.081	0.256
CRP (mg/l)		-0.045	0.532
Ferritin (ng/ml)		0.031	0.675
HDL (mg/dl)		-0.074	0.301
ESR (mm/l)		-0.032	0.652
NLR		-0.001	0.993
PLR		-0.053	0.456
MHR		0.069	0.336
*: p<0.05, t: Independent Samples T-Test, F: One-way analysis of variance (ANOVA), Difference: Tukey's multiple comparison test, r: Pearson's correlation coefficient, ICU: Intensive care unit, S.D.: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, HD: Heart disease, COPD: Chronic obstructive pulmonary disease, WBC: White blood cell (×103 µl), NEU: Neutrophils (×103 µl), LYM: Lymphocytes (×103 µl), PLT: Platelets (×103 µl), MON: monocytes (×103 µl), CRP: C-reactive protein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MHR: Monocyte/HDL ratio			

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Table 3. Relationship between the discharge status and other variables					
	1. Home	**2. ICU**	**3. Death**	**Chi-square**	**p**
	n (%)	n (%)	n (%)		
Gender					
Women	70(71.4)	10(10.2)	18(18.4)	3.179	0.204
Men	60(59.4)	15(14.9)	26(25.7)		
HT					
Yes	89(66.4)	15(11.2)	30(22.4)	0.701	0.704
No	41(63.1)	10(15.4)	14(21.5)		
DM					
Yes	42(59.2)	9(12.7)	20(28.2)	2.477	0.290
No	88(68.8)	16(12.5)	24(18.8)		
COPD					
Yes	20(64.5)	6(19.4)	5(16.1)	1.946	0.378
No	110(65.5)	19(11.3)	39(23.2)		
HD					
Yes	36(66.7)	6(11.1)	12(22.2)	0.145	0.930
No	94(64.8)	19(13.1)	32(22.1)		
	Mean ± S.D.	**Mean ± S.D.**	**Mean ± S.D.**	**F**	**p**
Age	74.98 ±7.51	74.36±9.87	75.45±7.76	0.155	0.856
WBC	6.46 ±2.67	7.83 ±3.22	9.33 ±8.58	6.320	**0.002*** **Difference: 1-3**
NEU	4.37 ±3.78	5.33 ±2.93	5.12 ±2.60	1.312	0.272
LYM	2.15 ±3.43	1.98 ±1.10	2.27 ±1.39	0.081	0.922
PLT	215.93 ±82.70	214.68±98.67	211.57±73.79	0.045	0.956
MON	0.57 ±0.38	0.70 ±0.85	0.65 ±0.44	1.021	0.362
D-Dimer	2.07 ±5.17	4.37 ±8.05	3.05 ±6.22	1.814	0.166
CRP	8.19 ±12.45	13.98 ±8.67	11.38 ±9.43	3.359	**0.037*** **Difference: 1-2**
Ferritin	365.98 ±374.77	657.56±513.43	526.53±481.61	6.147	**0.003*** **Difference: 1-2**
HDL	31.33 ±9.12	34.84 ±9.00	50.89 ±13.68	59.681	**0.000*** **Difference: 3-1.2**
ESR	59.93 ±19.52	59.36 ±17.54	69.30 ±17.72	4.297	**0.015*** **Difference: 1-3**
NLR	3.20 ±2.70	3.70 ±2.98	3.53 ±4.56	0.346	0.708
PLR	159.36 ±117.88	144.21±100.99	143.59±149.53	0.356	0.701
MHR	0.02 ±0.01	0.02 ±0.03	0.01 ±0.01	3.846	**0.023*** **Difference: 2-3**

*:p<0.05, F: One-way analysis of variance (ANOVA) Difference: Tukey's multiple comparison test, HT: Hypertension, DM: Diabetes mellitus, HD: Heart disease, COPD: Chronic obstructive pulmonary disease, WBC: White blood cell (×103 μl), NEU: Neutrophils (×103 μl), LYM: Lymphocytes (×103 μl), PLT: Platelets (×103 μl), MON: Monocytes (×103 μl), CRP: C-reactive protein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MHR: Monocyte/HDL ratio

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DISCUSSION

Aging is a major risk factor alone for serious disease and death from COVID-19. Age-related decline and dysregulation in immune functions and the emergence of comorbid diseases increase susceptibility in old age, leading to serious COVID-19 outcomes (13). The mean age of patients over the age of 65, who received treatment for COVID-19 in our inpatient service, was 75.01±7.86 years. Of our patients; 50.8% were men, 65.3% were discharged to home, and 22.1% died. Jihye Hwang et al. reported that, of the older adult patients that received treatment for COVID-19, 37.9% were men, 15% were nonsurvivors, and the remaining group was discharged to home (14).

Of our patients at the age of 65 years and over, who were treated as inpatients because of the diagnosis of COVID-19, the lengths of hospital stay of nonsurvivors and those patients, who were discharged to home, were significantly shorter than those, who were transferred to ICU. Compatible with our study results, Lang Wang et al. found in their study that the length of hospital stay was significantly shorter in older nonsurvivors (15). They showed that, in older nonsurvivors, the number of comorbid diseases was high, the prognosis was poor, the disease progression was rapid, and, consequently, the length of hospital stay was short. In our study, we found that the length of stay was also short in patients, who were discharged to home. We thought that this result occurred because patients were discharged to home as soon as possible after overcoming the life-threatening situation. The aim was to protect patients from hospital-related complications and avoid potential work intensity. We could not find a significant relationship between the comorbidities of the patients and the length of hospital stay but we found a low level of positive correlation between comorbidities and high WBC counts.

CRP is an acute phase protein and an important biomarker. CRP levels increase rapidly and significantly during acute inflammatory responses (16). The CRP level has been shown to be an effective parameter in predicting the intensity and the severity of COVID-19 pneumonia at an early stage (17,18). Of the patients we treated, CRP and ferritin levels of patients, who were transferred to ICU, were significantly higher than those, who were discharged to home. In a recent study, the pneumonia severity index (PSI) and CRP levels were found to be significantly higher in older adult patients compared to younger patients (19). Similarly, in another study, it was shown that

serum ferritin levels were higher in patients, who had severe disease and died (20).

Peripheral blood monocytes are the basic mononuclear cells that are in charge of the appropriate fight against pathogens including viruses. It has been reported that the normal range of the monocyte count in COVID-19 patients varies according to disease stages (21,22). HDL is an antioxidant and anti-inflammatory molecule that plays a role in the regulation of cholesterol transport between tissues. HDL is involved in the modulation of inflammation and oxidative stress (23). Recent studies have shown that MHR values may be a new marker of inflammation and oxidative stress (24). In our study, HDL levels were significantly higher in patients, who died with a diagnosis of COVID-19, while MHR rates were higher in patients, who were transferred to ICU. We thought that these results were associated with the inflammatory state and poor prognosis. In previous studies, high NLR and PLR values were defined as independent factors for poor prognosis in COVID-19 but we did not obtain significant NLR and PLR values in our study (25,26).

It has been shown that high levels of laboratory parameters including WBC, ESR, and CRP indicate the extent of inflammation and tissue damage in COVID-19 pneumonia (27,28). In our study, we found that the WBC count and erythrocyte sedimentation rates were significantly higher in nonsurvivors compared to patients, who were discharged to home. In their metaanalysis, Henry et al. concluded that patients with severe and fatal diseases had significantly increased WBC counts compared to survivors (20). In another study, ESR and the severity of pneumonia were positively correlated (29).

The limitations of our study were that we did not categorize the patients according to the severity of pneumonia and that we included a limited number of patients. More detailed evaluations with larger patient groups are required to obtain definitive results.

CONCLUSION

Geriatric patients are susceptible to adverse clinical outcomes of COVID-19. The evaluation and treatment are difficult in this age group. In this study, we observed significantly high levels of WBC, ESR, and HDL and a short duration of hospital stay in nonsurvivors compared to the rest of the patients over 65 years of age, who received treatment for COVID-19 pneumonia. We found that the CRP, ferritin, and MHR levels of the patients, who were

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transferred to ICU, were significantly high. In geriatric patients with COVID 19 pneumonia, these markers may be predictors of prognosis to be used during the treatment process and may predict the discharge status. In the management of COVID-19 infection in geriatric patients, it is necessary to understand such indicators of poor prognosis. Furthermore, screening procedures need to be implemented. This way, treatment can be started as soon as possible for such patients with unfavorable prognostic marker values.

DECLARATIONS

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Determining the Sensitivity in the Diagnosis of Preoperative Orbital Computed Tomography in Patients With Open Globe Injury and Evaluating the Affecting Factors

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ABSTRACT

Purpose: Open globe injuries are diagnosed by ophthalmological examination. The purpose of this study is to determine the sensitivity in the diagnosis of preoperative orbital computed tomography (CT) in our patients with open globe injury and to evaluate the affecting factors.

Materials and Methods: The data of patients who underwent open globe injury repair between September 2014 and February 2021 in the Akdeniz University Hospital Ophthalmology Clinic were retrospectively analyzed. Demographic data of 290 patients' were recorded. Patients suffer from corneal, scleral and corneoscleral injury; classified as pediatric and adult age groups. The presence of open globe injury, foreign body(FB) and orbital fracture in the preoperative orbital CT report were recorded.

Results: Sixty (20.7%) women and 230 (79.3%) men were included in the study. Of the patients, 58 (20%) were pediatric and 232 (80%) were adults. There were corneal, 76 (26.2%) scleral, and 59 (20.3%) corneoscleral injuries in 155 (53.4%) patients. In the preoperative orbital CT report, it was stated that 163 (56.2%) patients had open globe injuries. We did not observe any statistical difference between the diagnostic efficiency of orbital CT in pediatric and adult groups (p=0.636). When we evaluate according to the location of wound; scleral and corneoscleral injuries were compared with corneal injuries, we found that orbital CT was more effective in diagnosing (p<0.001). Similarly, as the length of wound increased, the diagnostic efficiency of orbital CT increased (p<0.001).

Conclusion: In this study, we found the sensitivity of orbital CT in diagnosing open globe injury as 56.2%. Diagnostic efficiency increases in the presence of scleral and corneoscleral injuries and a full-thickness incision greater than 4 mm. We found that age, gender, and presence of orbital fracture had no effect on the sensitivity of orbital CT in diagnosing open globe injury. It should be kept in mind that nearly half of the patients may miss the diagnosis by orbital CT.

Keywords: Open globe injury, Orbital CT, Trauma

Açık Glob Yaralanmalarında Orbital Bilgisayarlı Tomografinin Tanı Koymadaki Duyarlılığı ve Buna Etki Eden Faktörlerin Değerlendirilmesi

ÖZET

Amaç: Açık glob yaralanmalarının tanısı oftalmolojik muayene ile konulmaktadır. Bu çalışmanın amacı açık glob yaralanması olan hastalarımızda acil şartlarda istediğimiz preoperatif orbital bilgisayarlı tomografinin (BT) tanı koymadaki duyarlılığının saptanması ve buna etki eden faktörlerin değerlendirilmesidir.

Gereç ve Yöntem: Akdeniz Üniversitesi Hastanesi Göz Hastalıkları kliniğinde Eylül 2014 - Şubat 2021 tarihleri arasında açık glob yaralanması onarımı yapılmış hastaların verileri retrospektif olarak incelendi. Verilerine ulaşılabilen 290 hastanın demografik verileri kaydedildi. Hastalar korneal, skleral ve korneaskleral yaralanma; pediatrik ve erişkin yaş gurubu olarak sınıflandı. Preoperatif orbital BT raporundaki açık glob yaralanması, YC ve orbital fraktür varlığı kaydedildi.

Bulgular: Çalışmaya 60 (%20,7) kadın, 230 (%79,3) erkek dahil edildi. Hastaların 58'i (%20) pediatrik, 232'si (%80) erişkindi. 155 (%53,4) hastada korneal, 76 (%26,2) skleral ve 59 (%20,3) korneaskleral yaralanmaydı. Preoperatif çekilen orbital BT raporunda 163 (%56,2) hastada açık glob yaralanması olduğu belirtilmişti. Pediatrik ve erişkin gruplarda orbital BT tanı koyma etkinliği arasında herhangi bir istatistiksel fark izlemedik (p=0,636). Kesi yerine göre değerlendirdiğimiz zaman; skleral ve korneaskleral yaralanmalar korneal yaralanmalar ile karşılaştırıldığında orbital BT'nin tanı koyma etkinliğinin daha fazla olduğunu gördük (p<0.001). Benzer şekilde kesi uzunluğu artınca orbital BT'nin tanı koyma etkinliği arttı (p<0.001).

Sonuç: Bu çalışmamızda orbital BT'nin açık glob yaralanma tanısı koymadaki duyarlılığını %56,2 olarak bulduk. Skleral, korneaskleral yaralanmalar ve 8 mm üzerinde tam kat kesi varlığında tanı koyma etkinliği artmaktadır. Yaş, cinsiyet ve orbital fraktür varlığı orbital BT'nin açık glob yaralanması tanısını koymadaki duyarlılığına bir etkisinin olmadığını gördük. Hastaların yarısına yakınında tanıyı atlayabileceği akılda tutulmalıdır.

Anahtar kelimeler: Açık glob yaralanması, Orbital BT, Travma

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Open globe injuries are important causes of morbidity and monocular blindness (1,2). All full-thickness globe injuries are called open globe injuries (3,4). Clinical signs and symptoms include decreased visual acuity, hyphema, decreased anterior chamber depth, pupillary irregularity, hypotonia and prolapse of intraocular tissues. However, most cases of severe ocular trauma are both a diagnostic and treatment challenge to the ophthalmologist and emergency physicians (5,6). Findings such as eyelid edema and subconjunctival hemorrhage make ophthalmological examination and diagnosis difficult. In such cases, radiological imaging methods are used to support the diagnosis. Ultrasonography is contraindicated in cases that open globe injury is suspected (7). Magnetic resonance (MR) shows orbital soft tissues in detail, but is not used in trauma patients due to the risk of metallic intraocular foreign bodies (7).

Orbital computed tomography (CT) is the first-choice imaging modality to obtain information about the severity and extent of trauma in ocular trauma patients (8). It is particularly helpful in imaging orbital bone structures and fractures. In open globe injuries, it has been reported that the diagnostic sensitivity is between 56-75%, although it varies depending on the radiologist (8-10). Change in globe contour, decrease in globe volume, scleral irregularity, presence of air or foreign body in the globe are CT findings in open globe injury. The role of orbital CT in demonstrating orbital bone structures and foreign body presence in trauma patients is certain. In this study, we aimed to evaluate the sensitivity of orbital CT in diagnosis of open globe injury and the factors affecting sensitivity (10,11).

MATERIALS AND METHODS

In our study, the data of 290 patients who underwent primary repair due to open globe injury in Akdeniz University Hospital Ophthalmology department between September 2014 and February 2021 were evaluated retrospectively. Our study which was conducted in accordance with the principles of the Declaration of Helsinki was approved by local ethics committee of Akdeniz University Faculty of Medicine (KAEK:639 / 15.09.2021).

Demographic characteristics of the patients, localization and size of wound were recorded. The preoperative orbital CT report was obtained from hospital records. Increase or decrease in anterior chamber depth, scleral contour irregularity, absence of scleral wall integrity, decrease in globe volume, and presence of air or foreign body in the globe were passed for open globe injury. In addition, the presence of intraorbital foreign body and orbital fracture were also recorded. Depending on the location of the wound, the patients are classified by corneal, corneoscleral and scleral. According to age group, patients are classified by pediatric and adult. Patients who underwent open globe injury repair in our clinic and whose preoperative orbital CT data were accessed were included in the study. Patients whose primary repair was performed in an external center and data could not be accessed were excluded from the study.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 23.0 for Windows (IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov test was used for normality distribution. Continuous variables were given as mean ± standard deviation, and categorical variables were given as frequency (percentage). Comparisons between groups were made using the independent simple t-test on independent samples. Comparisons of categorical variables were evaluated with chi-square ($\chi2$) analysis. ROC analysis was used and cut-off values are calculated with area under the ROC curve (AUC). P value less than 0.05 was considered statistically significant.

RESULTS

290 eyes of 290 patients were included in the study. The demographic characteristics of the patients are summarized in Table 1. In gender distribution, open globe injuries were statistically higher in males ($p < 0.001$). The mean age was 35.76 ± 19.81 years; was 41.2 ± 9.1 in the adult group and 13.9 ± 4.2 in the pediatric group. We found that open globe injuries were more common in the adult age group compared to the pediatric age group ($p < 0.001$). In addition, we found that open globe injuries were more common in males in both pediatric and adult age groups ($p < 0.05$).

In the preoperative orbital CT reports, 163 (56.2%) patients had open globe injuries; it was also stated that 61 (21%) patients had foreign bodies and 10 (3.4%) patients had orbital fractures.

When we evaluate according to the wound site; we found that the diagnostic efficiency of orbital CT was higher in scleral and corneoscleral injuries compared to corneal injuries ($p < 0.001$). Similarly, there was a positive correlation between the wound length and the diagnostic efficiency of orbital CT ($p < 0.001$). Especially, we used ROC analysis

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and performed that orbital CT diagnoses open globe injury with a higher rate in wounds larger than 4 mm, while the success of diagnosis decreases in wounds of 4 mm and smaller (AUC = 0.885, p < 0.001).

58 patients were in pediatric group and 232 patients were in the adult group that we repaired as open globe injuries. We found orbital CT sensitivity 53.5% in the pediatric group and 56.7% in the adult group. In terms of gender distribution, the sensitivity of orbital CT was 51.7% in women and 57.4% in men. Sensitivity of orbital CT was 52.8% in the group with orbital fracture and 53.7% in the group without fracture. We found that age, gender, and presence of orbital fracture had no effect on the sensitivity of orbital CT in diagnosing open globe injury (p = 0.636, p = 0.426, p = 0.707, respectively).

Table 1. Demographic characteristics of patients		
Gender (n (%))	**Male**	230 (79.3%)
	Female	60 (20.7%)
Age (n (%))	**Adult**	232 (80%)
	Pediatric	58 (20%)
Age (mean, years)		35.76 ± 19.81
Lenght of the wound (mm)		6.11 ± 3.79
Location of the wound (n (%))	**Corneal**	155 (53.4%)
	Corneoscleral	76 (26.2%)
	Scleral	59 (20.3%)

DISCUSSION

Birmingham Eye Trauma Terminology defines full-thickness eye injuries as open globe injuries (2). Open globe injuries are an important public health problem resulting in vision loss in both developed and developing countries. The diagnosis of open globe injury is made by the presence of a full-thickness globe tissue injury. Depending on the type and severity of the trauma, it may become very difficult to diagnose, especially in blunt traumas. Radiological imaging methods are used to support the diagnosis.

Orbital CT is preferred as the first choice imaging method in trauma patients in emergency conditions. Orbital CT provides information about globe integrity, presence of foreign body and orbital bone structures. Orbital CT is not valuable as clinical examination when anterior segment

details are clear. However, increase or decrease in anterior chamber depth, scleral contour irregularity, absence of scleral wall integrity, decrease in globe volume and presence of air or foreign body in the globe in orbital CT are the findings suggesting open globe injury (8,12-14).

In this study, we found the sensitivity of orbital CT in diagnosing open globe injury as 56.2%. This rate has been reported to be between 56-75% in previous studies (8-10). In open globe injuries that are not clinically obvious, the rate falls to the range of 56-68% (8). Although the rate in our study is relatively low, we see that it is similar to previous studies. In our study, orbital CT reports were analyzed retrospectively and these reports consist of reports that are rapidly evaluated in emergency conditions. It has been suggested in the literature that this rate difference may be due to the experience of the interpreting radiologist (10,15,16).

When we consider age distributions, we did not see any statistical difference in the diagnostic efficiency of orbital CT between the pediatric group and the adult group. The globe is smaller in the pediatric age group. We concluded that this size difference does not increase the risk of missing the diagnosis with imaging methods. Likewise, gender and the presence of orbital fracture did not make a significant difference in the diagnostic efficiency of orbital CT.

When we evaluated according to the wound sites, we saw that the diagnostic efficiency of orbital tomography was lower in corneal injuries. There is a change in anterior chamber depth in corneal wounds generally. In emergency conditions, anterior chamber depth is evaluated cursory in orbital CT reports. Therefore, the diagnosis of isolated corneal open globe injuries may be missed. Joseph et al. reported that the rate of change in anterior chamber depth on orbital CT in open globe injuries was 48-86% (15). Therefore, inconspicuous changes in anterior chamber depth can be missed in the orbital CT report evaluated in emergency conditions.

When we consider the length of the wound site, we observed that the diagnostic efficiency of orbital CT increased especially in cases with a diameter of 4 mm and above. As the wound length increases, the effect of the globe increases; therefore, the visibility of existing findings in orbital CT also increases.

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The limitation of the study is retrospective design and relatively small number of patients included. Data included in the study were selected to test the sensitivity of imaging-based diagnosis. There are many studies in the literature evaluating the sensitivity of orbital CT in open globe injuries; however, we did not find a study examining the factors affecting sensitivity. We suggest that this study is important because it has look from a different perspective about the subject.

In conclusion, open globe injuries are an ophthalmologic emergency diagnosed by clinical examination. Orbital CT is the first-choice imaging method that can be performed in trauma patients in emergency conditions. The sensitivity of orbital CT in diagnosing open globe injury is similar in pediatric and adult age groups. Similarly, gender and the presence of orbital fracture do not affect sensitivity. Diagnostic efficiency increases in the presence of scleral and corneoscleral injuries and a full-thickness wound greater than 4 mm. Although orbital CT is not the first choice in diagnosing open globe injury, it is important in terms of supporting the diagnosis and detecting foreign body and orbital fracture. It should also be kept in mind that orbital CT may miss the diagnosis in nearly half of open globe injuries.

DECLARATIONS

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

Ethical Approval
This study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (KAEK:639 / 15.09.2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Availability of Data and Material
All data and material are available on request from the authors. The data that support the findings of this study are available from the corresponding author, [A.Ç.Y.], upon reasonable request.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

The Effect of Deformity on Functional Scores in Humerus Shaft Fractures Treated With Functional Bracing

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ABSTRACT

Purpose: The aim of the study is to evaluate the effect of deformity on functional scores of humeral shaft fracture patients who treated conservatively with functional bracing.

Methods: Patients who had humeral shaft fracture and treated with functional bracing between 2014 and 2019, were included in this study. Second or third day, two part functional brace was applied. The deformity angle of the humerus on the anteroposterior and lateral radiography was measured and divided into 3 groups. Elbow range of motion (ROM), shoulder abduction and the difference of range of external rotation (ER) compared to contralateral shoulder was evaluated. Moreover, Constant scores of the shoulder and Mayo scores of the elbow were evaluated.

Results: Forty-two patients were evaluated. The mean healing time was determined as 12.11 ± 2.31 weeks. Thirty-seven of the patients were successfully treated. Nonunions were detected in only 5 patients during follow-up. The varus deformity was measured between 6°-10° in 18 patients, >11° in 12 patients, and between 0°-5°in 7 patients. In the varus deformity groups, a statistically significant difference was observed for the external rotation measurements (p:0.044) and for elbow ROM measurements (p: 0.048). The reason of the external rotation and elbow ROM measurements difference was >11° varus deformity group. There was no statistically significant difference between the shoulder abduction range, Mayo scores and shoulder constant scores of the varus deformity groups (p>0.05).

Conclusion: Our clinical and radiological datas show that satisfactory results are obtained in most of the humeral shaft fractures treated with functional bracing.

Keywords: Humeral shaft fractures, functional bracing, nonoperative treatment of Humerus fractures

Fonksiyonel Breys ile Tedavi Edilen Humerus Şaft Kırıklarında Deformitenin Fonksiyonel Skorlar Üzerine Etkisi

ÖZET

Amaç: Bu çalışmanın amacı, fonksiyonel breys ile konservatif tedavi edilen humerus cisim kırığı hastalarında deformitenin fonksiyonel skorlar üzerindeki etkisini değerlendirmektir.

Yöntem: 2014-2019 yılları arasında humerus cisim kırığı olan ve fonksiyonel breys ile tedavi edilen hastalar bu çalışmaya dahil edildi. Kırıktan sonra ikinci veya üçüncü gün, iki parçalı fonksiyonel korse uygulandı. Ön-arka ve yan radyografilerde humerusun deformite açısı ölçüldü ve 3 gruba ayrıldı. Dirsek hareket açıklığı(EHA), omuz abdüksiyonu ve karşı omuza göre dış rotasyon açıklığı farkı değerlendirildi. Ayrıca omuz Constant skorları ve dirsek Mayo skorları değerlendirildi.

Bulgular: 42 hasta değerlendirildi. Ortalama iyileşme süresi 12.11 ± 2.31 hafta olarak belirlendi. 37 hasta başarıyla tedavi edildi. Takiplerde sadece 5 hastada kaynamama saptandı. Varus deformitesi 18 hastada 6°-10°, 12 hastada >11° ve 7 hastada 0°-5° arasında ölçüldü. Varus deformitesi gruplarında dış rotasyon ölçümlerinde (p:0.044) ve dirsek EHA ölçümlerinde (p:0.048) istatistiksel olarak anlamlı fark gözlendi. Dış rotasyon ve dirsek EHA ölçümleri farkının nedeni >11° varus deformitesi grubuydu. Varus deformitesi gruplarının omuz abdüksiyon aralığı, Mayo skorları ve omuz constant skorları arasında istatistiksel olarak anlamlı fark yoktu (p>0.05).

Sonuç: Klinik ve radyolojik verilerimiz fonksiyonel breys ile tedavi edilen humerus cisim kırıklarının çoğunda tatmin edici sonuçlar alındığını göstermektedir.

Anahtar kelimeler: Humerus şaft kırıkları, fonksiyonel breys, humerus kırıkları cerrahi dışı tedavi

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Humeral shaft fractures account for 1-3% of all adult fractures (1,2). And incidence is about 10-20/100.000 person-years. In elderly patients it increases up to 100/100000 (3,4). Generally causes of humeral shaft fractures are simple falls, sport injuries and traffic accidents (5).

There is a consensus that most of the humerus shaft fractures can be treated by conservative methods (2,3). And functional bracing treatment is the most widely used method for acute, isolated and closed humeral shaft fracures (3). On the other hand surgery is recommended in case of neurovascular injuries, open fractures, multitrauma, floating elbow, bilateral humeral shaft fracture, pathological fracture, improper reduction and brachial plexus or vascular pathology with humeral shaft fracture (4,5). The most important advantage of the open reduction is visualization of fracture sites for anatomic reduction. Also, different complications can occur. Such as pseudoarthrosis, infection, shoulder stiffness, axillary nerve palsy, radial nerve palsy, tendon injuries and implant failure (6,7).

The treatment firstly requires follow-up for approximately 2 weeks in a well molded splint. Then a functional brace is used. Sarmiento et al. popularized that procedure in 1970's. Working principles of the humeral functional braces are circumferentially compression effect, active contraction of the muscles and gravity effect. Functional bracing allows full range of motion at the shoulder and elbow joints and good or excellent outcomes. Moreover, shoulder function problems, malunion, and non-unions were reported after conservative treatment (8,9). Nonunion with a functional bracing is rare. However, it occurs commonly in the proximal third of humeral shaft fractures (10).

Functional bracing treatment for humeral shaft fractures is a challenging process for the physician and patient. In the first 3-6 weeks, patients are followed up in weekly outpatient controls. It is checked whether the angulation is within acceptable limits with radiographs (11). Acceptable limits are maxium 3 cm shortening, 20° anterior-posterior angulation and 30° varus-valgus angulation and 15° malrotation.

The aim of the current study is to evaluate the effect of deformity on functional scores of humeral shaft fracture patients who treated conservatively with functional bracing.

MATERIALS AND METHODS

Patients who had humeral shaft fracture and treated with functional bracing between November 2014 and December 2019, were included in this study. The study was approved by the Institutional Review Board. Patients data records and radiographic images were analyzed retrospectively. Patients age, sex, fracture site, mechanism of injury, and duration of fracture union were recorded.

Proximal and distal humerus fractures, bilateral humerus fractures, polytraumatised patients, neurovascular injury, patients under 18 and over 85 years, intraarticular fractures, pathologic fractures, open fractures, humeral shaft fracture with shoulder or elbow pathologies, another trauma affecting the same extremity, and prior shoulder, humerus or elbow surgery were excluded from the study.

At the beginning, all patients were immobilized with a U splint and an arm sling. After that patients were followed up in the outpatient clinic. When the pain and edema of the arm subsided, two part functional brace was applied about second or third day (Figure 1). The brace was fitting properly to the soft tissue curves and creases of the arm. It was fitted by an orthopedic surgeon and plaster technician who was experienced. The same brace was applied to all humeral shaft fractures. After aplication of the brace, fracture reduction was evaluated in control humerus AP and lateral radiographs. Rehabilitation was started in patients whose reduction was within acceptable limits. Pendular shoulder exercises and flexion and extension of the elbow was begun immediately. After 3 weeks passive range of motion (ROM) exercises of shoulder started. After 6 weeks active exercises and after 9 weeks scapulohumeral rhythm exercises were started. In order to avoid the angulation of fracture patients were told not to lean on their elbow and abduct the shoulder. Except the times spent for personal hygiene, functional orthesis was used for all the time. The brace was used until bony union.

In the first month, patients were followed up every week, after the first month twice a month. In all outpatient clinic controls, radiological evaluations of the patients were performed on AP and lateral humerus radiographs. The functional bracing treatment was ended after the clinical and radiological fracture union was achieved. Union was defined when there was no pain and abnormal movement at the fracture site and radiologically bridging between the fragments was visualized.

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Figure 1: Functional brace

At the outpatient control, the deformity angle on the anteroposterior x-ray was measured and coronal plane deformities were divided into three groups, namely 0°-5°, between 6°-10°, and >11° varus. And the deformity angle on the lateral x-ray was measured ande sagittal plane deformities were divided into three groups, namely 0°-5°, between 6°-10°, and >11° extension/flexion (ext/flex) deformity. X-ray images of one patient are shown below (Figure 2). And elbow range of motion (ROM), shoulder abduction and the difference of range of external rotation (ER) compared to contralateral shoulder was evaluated. Constant scores of the shoulder and Mayo scores of the elbow were evaluated. In addition, complications were recorded.

Statistical Analysis

Statistical analysis was performed by using SPSS 22.0 version software program for Windows. Shapiro Wilks test was used to determine parameters distribution. Kruskal Wallis test was used for comparison of qualitative data between the groups and Mann Whitney U test was used to determine the difference between the groups. Mann Whitney U test was also used to compare the parameters between the two groups. In order to analyze the relation between the parameters Spearman's rho correlation analysis was used. The results were evaluated within the 95% confidence interval and P <0.05 was considered as statistically significant.
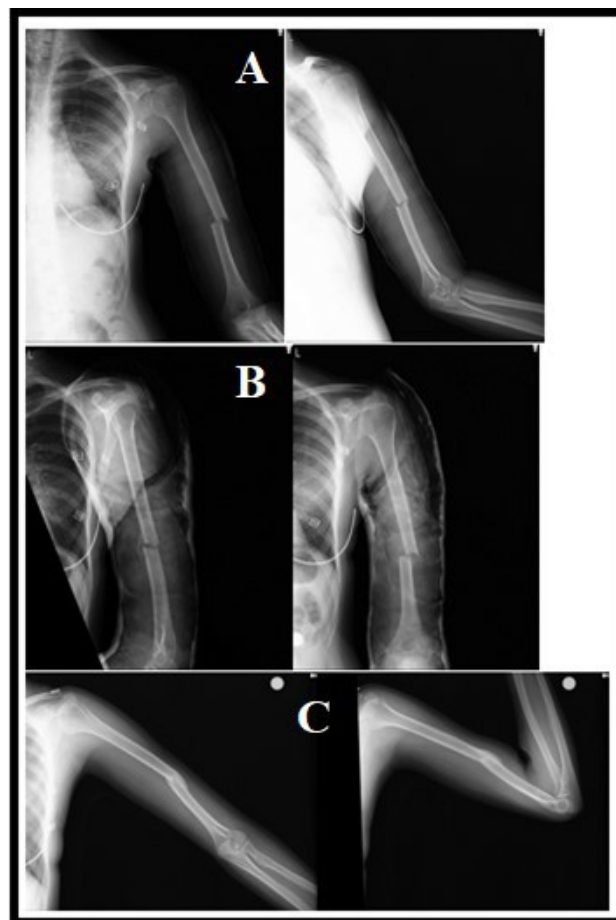
Figure 2: Outpatient control radiographies (A: inital radiographies, B: first month radiograhies, C: first year radiographies)

RESULTS

In the current study, 55 humeral shaft fracture were treated with functional bracing. Forty-two of the patients data records were obtained. The mean age was 53.43 ± 16.88 (22-85) years. Twenty-three patients had a right sided fracture and the remaining 14 patients had left sided fracture. The mechanism of injury of 24 patients was simple fall, 11 patients suffered traffic accident, and 2 patients had forensic incident. Sixteen patients had comorbidity. Nine of them had hypertension, 3 of them had hypertension and diabetes, 2 of them had hypertension and chronic pulmonary disease, one of them had chronic pulmonary disease and diabetes and the remaining one had Parkinson, chronic pulmonary disease and hypertension (Table 1).

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Table 1: Demographic characteristics of the patients	
Gender (Male / Female)	22 / 15
Age (years)	53.43 ± 16.88 (22-85)
Fracture side (Left / Right)	14 / 23
Mechanism of injury	
Simple fall	24
Traffic accident	11
Forensic incident	2
Comorbidity (Yes / No)	16 / 21

The mean healing time was 12.11±2.31 (8-16) weeks. Thirty-seven (22 male, 15 female) of the patients included in the study were successfully treated. Nonunions were detected in only 5 patients during follow-up (Table 2). The radial nerve injury was determined in two patients who were completely healed in their follow-up.

The varus deformity was measured between 6°-10° in 18 patients, >11° in 12 patients, and between 0°-5° in 7 patients. The flexion/extension deformity was measured as 6°-10° in 13 patients, >11° in 9 patients, and between 0-5 ° in 15 patients (Table 2).

The mean value for shoulder external rotation was -7.84° ± 6.62 (-20-0), for abduction 110.81° ± 11.64 (90-120). The mean value for elbow ROM was 134.32° ± 12.59 (110-150). Elbow Mayo scores mean value was 86.97 ± 6.22 (75-95) and for the shoulder Constant score it was 77.51 ± 4.57 (70-85) (Table 2).

In the varus deformity groups, a statistically significant difference was observed for the external rotation measurements (p=0.044). In order to determine which group caused the difference Mann-Whitney U test applied. There was no statistically significant difference between external rotation measurements of the varus deformity groups 6°-10° and 0°-5° (p=0.516). But a statistically significant difference was determined between >11° and the other varus deformity groups (p1= 0.030; p2= 0.046). The reason of the external rotation measuremnt difference was >11° varus deformity group. External rotation of the >11° varus group was more restricted.

Moreover, in the varus deformity groups, there was a statistically significant difference for elbow ROM measurements (p= 0.048). Mann-Whitney U test performed to detect which group caused the difference. There was no statistically significant difference between the elbow ROM measurements of the varus deformity groups 6°-10° and >11° (p= 0.082). But a statistically significant difference was determined between >11° and 0-5° varus deformity groups (p=0,027). The reason of the elbow ROM measurement difference was >11° varus deformity group. Elbow ROM of the >11° varus group was more restricted like external rotation.

Table 2: Clinical and functional scores of patients		
Healing time (weeks)		12.11 ± 2.31 (8-16)
Union		37
Nonunion		5
Varus deformity	Varus deformity 0°-5°	7
	Varus deformity 6°-10°	18
	Varus deformity >11°	12
Extension / Flexion deformity	Ext / Flex deformity 0°-5°	15
	Ext / Flex deformity 6°-10	13
	Ext / Flex deformity >11°	9
Shoulder ER limitation		-7.84 ± 6.62 (-20-0°)
Shoulder abduction		110.81 ± 11.64 (90-120°)
Elbow ROM		134.32 ± 12.59 (110-150°)
Elbow Mayo Score		86.97 ± 6.22 (75-95)
Shoulder Constant Score		77.51 ± 4.57 (70-85)
ER: External rotation, ROM: Range of motion		

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A statistically significant difference was not determined between shoulder abduction range, Mayo scores, and shoulder constant scores of varus deformity groups (p>0.05).

There was no statistically significant difference between the shoulder abduction measurements, elbow ROM measurement, elbow Mayo scores, and shoulder Constant scores of the extension/flexion deformity groups (p>0.05).

There was no statistically significant relationship between the age of the patients and external rotation and elbow ROM measurements (r= 0.284; p>0.05). Although, a negative relationship was determied between age of the patients and shoulder abduction measurement, shoulder Constant scores and elbow Mayo scores (r= 0.702; p= 0.001 and r= 0.458; p= 0.004, respectively).

A statistically significant relationship was not determined between age and shoulder abduction measurement, external rotation, shoulder Constant score and elbow ROM (p>0.05). Also, statistically significant relationship was not determined between fracture side and shoulder abduction, external rotation, elbow ROM, shoulder Constant, and elbow Mayo scores (p>0.05). Elbow Mayo scores of the male patients were higher (p= 0.018).

DISCUSSION

For the management of humerus shaft fractures, functional bracing is still the first choice and gold standard treatment method. Functional bracing for humeral shaft fractures provides high rate of fracture union, good functional results, patient comfort, and less expenses. Also, it provides avoiding the complications of surgical treatment (12). In the literature, the union rate of humerus shaft fracture with functional bracing is between 77.4-100% (13,14) and the healing time is between 7-12.6 weeks (8,14). In the current study the healing rate was 90.47% and the mean healing time was 12.11 ± 2.31 weeks. The rate of follow up was 76.36% and it was smilar to previous studies (7).

The most common complication with functional bracing is angular deformity of the arm and the most common deformity is varus angulation (15,16). In the literature, varus angulation is usually between 4°-9 ° (13,16). The angulation in sagittal plane is between 3°-6.2° (13,16). In our current study, average varus angulation was 8.72 ± 3.1°. No valgus deformity was determined in radiographies. Sarmiento et al. obtained %3 valgus deformity in 69 healed fracture (17).

Full shoulder range of motion can be achieved in 55-93% of patients (15,16). External rotation is usually affected in humeral shaft fractures which are treated with functional bracing. However, the limitation of this movement is rarely above 10° (6,7,15). In the current study, the limitation of ER was 7.84° ± 6.62 and the average shoulder abduction was 110.81° ± 11.64.

In the different studies, full elbow ROM is obtained with functional bracing in 76-100% of the patient (6,7,15,16). The most commonly limited movement in the elbow is flexion, but the limitation of flexion is rarely above 10 ° (6,13). In the current study, the elbow flexion were 134.32° ± 12.59 and it is consistent with the literature.

In the literature, different functional bracing systems were used for treatment of humeral shaft fractures. Unlike sarmiento, we used two piece brace, which was easier to use. Good and excellent results were reported for 80.7-100% of patients (6-7). In our study, the mean shoulder Constant score was 77.51 ± 4.57.

Functional bracing does not provide anatomical reduction but provides a cosmetically and psychologically acceptable alignment (7,16,18). Generally, residual deformity is seen in patients with short and obese arms (15). And varus angulation is commonly seen. In the current study, the shoulder external rotations and elbow ROM measurements are limited in the patients with > 11° varus deformity compared to other groups. However, shoulder abduction, Constant scores, and elbow Mayo scores are not affected by varus deformity. Extension/flexion deformity does also not affect shoulder external rotation, shoulder abduction, Constant scores and elbow Mayo scores.

The current study has some limitations. Firstly, the study was designed retrospectively. Secondly, limited number of the patients included in the study. Thirdly, more specific subgroups could be formed according to the localization and shape of the fracture. Another limitation of the study is the lack of the control group.

In conclusion, sagittal plane deformities don't affect shoulder and elbow joint ROM in the patients who have humeral shaft fracture and treated with functional bracing. Shoulder Constant Scores and elbow Mayo Scores do not change in the patients with varus deformity greater than 11°. However, it may cause limitation in elbow ROM and shoulder external rotation. Our clinical and radiological datas show that satisfactory results are obtained in most of the humeral shaft fractures treated conservatively with functional bracing.

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DECLARATIONS

Conflict of Interest

No conflicting relationship exists for any author.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Evaluation Of Information About Orthopeadic Diseases In Youtube Turkish Content: What Do Turkish-Speaking Patients Learn From Youtube About Rotator Cuff Surgery?

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ABSTRACT

Purpose: Our study aims to evaluate the quality and reliability of video sources about rotator cuff rupture treatment from Turkish YouTube sources.

Methods: On October 5, 2020, searches for "rotator cuff ameliyatı" ("rotator cuff surgery" in Turkish) and "rotator cuff onarımı" ("rotator cuff repair" in Turkish) were conducted on YouTube ® (http://www.youtube.com). The first 100 videos for both were collected. The quality and reliability of the videos were evaluated by using the DISCERN score, JAMA benchmark criteria, and YouTube Rotator Cuff Specific Score (RCSS).

Results: Among 200 videos, 94 videos were included. The video source was a physician or hospital in 62 (66.6%) cases, allied health professionals in 16 (16.65%) cases, and patients in 16 (16.65%) cases. DISCERN, JAMA, and RCSS scores were significantly higher for physician videos compared to the others. There was no significant correlation between the time since the upload of the video and the DISCERN and RCSS scores.

Conclusion: The Turkish videos on rotator cuff surgery that we accessed using the YouTube search engine were insufficient to properly inform patients.

Keywords: Health information, Internet, Accuracy, Rotator cuff surgery

Türkçe YouTube İçeriklerindeki Ortopedik Bilgilerin Değerlendirilmesi: Türkçe Konuşan Hastalar Rotator Kaf Ameliyatı Hakkında Neler Öğreniyor?

ÖZET

Amaç: Çalışmamızın amacı rotator cuff cerrahisi ile ilgili Türkçe YouTube kaynaklarının kalitesini ve güvenilirliğini incelemektir.

Yöntem: 5 Ekim 2020 tarihinde YouTube arama motorunda "rotator cuff ameliyatı" ve "rotator cuff onarımı" aramaları yapıldı. İki aramadan da ilk 100 video toplandı. Kalite ve güvenilirlik DISCERN, JAMA ve YouTube rotator cuff spesifik skorları kullanılarak değerlendirildi.

Bulgular: 200 video incelendi ve dahil etme kriterlerine uyan 94 video dahil edildi. Videoların 62 (%66.6) tanesi hekim kaynaklı, 16 (%16,65) tanesi diğer sağlık personeli kaynaklı, 16 (%16,65) tanesi ise hasta kaynaklı olduğu gözlendi. DISCERN, JAMA ve rotator cuff spesifik skorları hekim kaynaklı videolarda daha yüksek bulundu. Yüklenme tarihine göre DISCERN ve rotator cuff spesifik skorlarının anlamlı fark göstermediği görüldü.

Sonuç: YouTube arama motorunu kullanarak erişilen rotator cuff ameliyatı ile ilgili Türkçe videolar hastaları gerektiği gibi bilgilendirmek için yetersiz bulunmuştur.

Anahtar kelimeler : Sağlık bilgileri, İnternet, Doğruluk, Rotator cuff ameliyatı

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As the knowledge of and desire to learn about diseases increase, the practice of medicine enters a new era (1). Access to the internet is growing worldwide, and Internet users frequently conduct health-related research (2). However, the internet contains incomplete and inaccurate information and this poses a public health problem since there are no auditing institutions that regulate online health information (3). YouTube is the most used source for visual information about medical topics (4). Patients often refer to YouTube for medical and surgical information.

Rotator cuff repair is one of the most common orthopedic surgical procedures (5). YouTube is an essential resource for patients who are currently researching this treatment (6). In order to better understand the concerns, preferences, and questions of patients, it is necessary to examine the sources of their knowledge. Patients' obtaining information about their diseases from inadequate and inappropriate sources delays their application to treat and affects the expectations of patients about treatment.

There are studies in the literature investigating the reliability of the information in English videos on orthopedic diseases (6,7). These studies were conducted with English sources. However, Internet resources in different languages have different features. Our study aims to evaluate the reliability of video sources about rotator cuff rupture treatment from YouTube sources. We hypothesize that the videos do not provide sufficient quality and reliability for patients.

MATERIAL and METHODS

On October 5, 2020, searches for "rotator cuff ameliyatı" ("rotator cuff surgery" in Turkish) and "rotator cuff onarımı" ("rotator cuff repair" in Turkish) were conducted on YouTube ® (http://www.youtube.com). The first 100 videos for both were collected, assuming that users would not look beyond the fifth page of results (6,8). Recurring videos, non-audio videos, videos not related to surgery, irrelevant videos, videos of less than a minute in length, and videos with fewer than 1000 views were excluded (Figure 1). This study was conducted according to the principles of the Declaration of Helsinki.

The number of videos included, the length and viewing records of the videos, and their likes, dislikes, and upload times were recorded. According to the providers, videos were classified as originating from physicians or hospitals, from allied professionals (medical professionals such as physical therapists), and patients.

The quality and suitability of videos were assessed using the DISCERN score. DISCERN evaluates the quality of a publication with 16 questions. The first eight questions evaluate the reliability of the publication, the following questions address specific details about treatment options, and the last question evaluates the average quality. Each question is scored from 1 to 5 points from "no" to "yes." If the answer is "absolutely yes," 5 points are given, while 1 point represents "absolutely no." Scores of 63–75 points are classified as excellent, 51–62 as good, 39–50 as medium, 27–38 as insufficient, and 16–26 as very insufficient (9). JAMA benchmark criteria were used to measure the reliability, suitability, and usefulness of the videos (10). This evaluation includes whether there are authorship, source, date, last update, and related explanations (sponsorship, conflicts of interest, for-profit organization partnerships). Each criterion is scored with 1 point. The transparency and reliability of information are evaluated. The specific quality of diagnostic and surgical information of rotator cuff videos was assessed using the YouTube Rotator Cuff Specific Score (RCSS) that showed excellent ICC scores and a positive correlation with the DISCERN prepared in a similar study (6). One point is assigned for each criterion, resulting in a maximum possible score of 25 points. Video quality was categorized as excellent (21–25), good (16–20), fair (11–15), poor (6–10), or very poor (0–5). The criteria evaluated in the scoring are given in Table 1. The video power index (VPI) was calculated to assess the popularity of the videos using [like ratio × view ratio/100] (8). The view ratio was calculated as [number of views/time since upload]. No institutional review board approval was required for the study.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics for numerical variables are expressed as mean, standard deviation, median, and min–max values. In the normality analysis, nonparametric test procedures were run for the duration, VPI, DISCERN, and RCSS values, which did not show normal distribution in the Shapiro–Wilk test. In order to determine the relationships between parameters, the nonparametric alternatives of variance analysis, the Kruskal–Wallis test, and Spearman's rho correlation analysis were used. Correlation was classified as poor (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or excellent (0.81–1.00). The results were evaluated at 95% confidence intervals, and a value of 0.05

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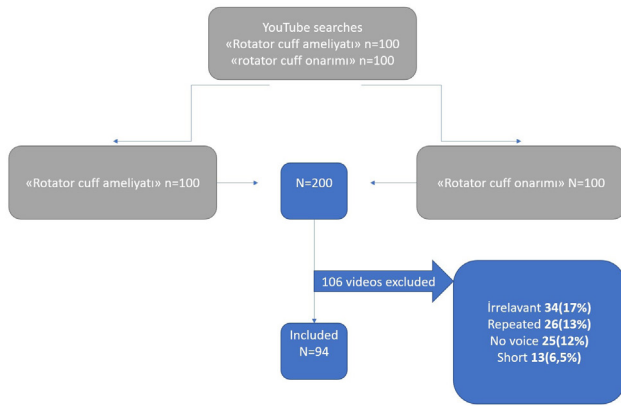
Figure 1. Flowchart of study

Table 1 Rotator Cuff Surgery YouTube Score (RCSS).	
	Points
Presurgery	
Anatomy of the rotator cuff timing	Max 1 point
Age	Max 1 point
Gender	Max 1 point
Characteristics of pain	Max 1 point
Clinical Tests	Max 1 point
Imaging	Max 1 point
Differential diagnosis	Max 1 point
Initial management	Max 1 point
Surgical contraindications	Max 1 point
Associated injuries	Max 1 point
Functional disability	Max 1 point
Surgical indications	Max 1 point
Functional disability	Max 1 point
During surgery and postsurgery	
Position	Max 1 point
Approach	Max 1 point
Technique	Max 1 point
Implant type and description	Max 1 point
Biologic preparation	Max 1 point
Presentation of the repair	Max 1 point
Additional procedures	Max 1 point
Description of the immobilization	Max 1 point
Description of the rehabilitation	Max 1 point
Description of the complications (Re-rupture, Stiffness, Infection, Implant related problems, Anesthesia related problems, Chronic shoulder pain)	Max 2 points (0,5 point for each 3 complications

RESULTS

A total of 200 websites resulting from the searches were analyzed, but 106 videos did not meet the inclusion criteria (irrelevant: 34 (17%), repeated: 26 (13%), no voice: 25 (12%), short: 13 (6.5%)) and, therefore, 94 videos evaluated. The baseline characteristics of the videos are shown in table 2.

The video source was a physician or a hospital in 62 (66.6%) cases, allied health professionals in 16 (16.65%) cases, and patients in 16 (16.65%) cases. According to the DISCERN score, 20 (21%) videos were good, 10 (11%) were fair, 24 (26%) were poor, and 40 (42%) were very poor. The RCSS showed that four (4%) videos were good, eight (8%) were fair, 22 (23%) were poor, and 60 (65%) were very poor. The DISCERN, JAMA, and RCSS scores were significantly higher for physician videos compared to the others (p<0.01, p=0.008, p<0.01). There was no statistical difference between the groups in terms of VPI (p>0.05).(Figure 2)

The average time from the upload of the video to the review was 1045 days. There was a significant negative correlation between the duration of the video and the VPI (r=-0.477). There was no significant correlation between the time since the upload of the video and the DISCERN and RCSS scores. The mean VPI of the videos was 51.7. There was no significant correlation between VPI and DISCERN and RCSS scores. There was a significant and positive high level of correlation between DISCERN and RCSS. (Table 3)
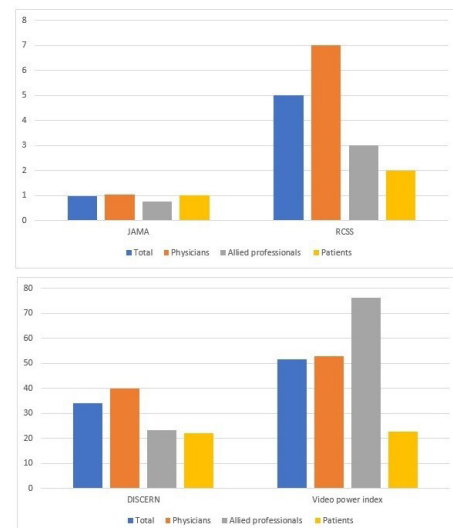
Figure 2. JAMA, RCSS, DISCERN scores and video power index of videos.

Table 2: Features of searched videos associated with rotator cuff *					
	Mean	Median	Maximum	Minimum	Standart deviation
DISCERN	34,02	32,00	56,00	18,00	13,91
JAMA	0,98	1,00	2,00	0,00	0,33
RCSS	5,6	4,00	18,00	1,00	4,2
Duration	272,5	133,00	2138	60	433,02
Likes	48,9	35,00	554,0	1,00	84,42
Dislikes	6,25	1,00	80,00	0,00	14,28
Time since upload	1045,5	1213,00	2868,00	17,00	671,99
Views	27354,1	10244,00	219230,00	1000	50646,90
Video power index	51,71	23,55	357,33	1,06	77,70
*: words used in search : "rotator cuff onarımı, rotator cuff ameliyatı"					

Table 3: Correlation Coefficient values between video features and scores					
			Video power index	DISCERN	RCSS
Spearman's rho	Time since upload (days)	Correlation Coefficient	-0,477	-0,071	-0,103
		Sig. (2-tailed)	0,000	0,494	0,324
	Video power index	Correlation Coefficient		-0,157	-0,092
		Sig. (2-tailed)		0,132	0,375
	DISCERN	Correlation Coefficient			0,702
		Sig. (2-tailed)			0,000

DISCUSSION

The main finding of this study is that YouTube videos on rotator cuff surgery are insufficient. None of the videos were excellent according to the DISCERN and RCSS scores, and 64% of the videos were poor or very poor according to DISCERN while 88% were poor or very poor according to the RCSS. Our findings support the studies in the literature on English videos. In the study by Celik et al. (6) examining videos about rotator cuff surgery in English, DISCERN and RCSS scores were reported as poor and very poor at rates of 76% and 84%, respectively. Cassidy et al. (7) evaluated videos on anterior cruciate ligament

reconstruction on YouTube and reported that most of the videos were of low quality. In the study by Kunze et al. (11), they evaluated meniscus videos on YouTube and reported that the videos were of low quality. In a study by Ceyhan et al. (12) examining Turkish orthopedic sites accessed through search engines, it was reported that the sites were inadequate and of poor quality and the scores were even lower than the scores reported for English sites. The scores achieved in the current study are similar to those in studies in which English videos were evaluated.

It was observed that physicians provided 66% of the videos. In other studies in the literature, it was likewise reported that the primary providers of videos were physicians (6,7,11). It has been observed that the quality of the videos provided by physicians is higher than that of other providers (6,7,11,13). However, the average DISCERN score for the physician videos, representing the best group, was only considered fair, while the average RCSS score was poor. When the data are reviewed, it is observed that our hypothesis is verified and these video sources are far from providing sufficient information to patients.

The VPI, defined by Erdem et al. (8), was calculated in order to evaluate individuals' interest in the videos. There was no correlation between DISCERN scores or the RCSS and VPI, which shows that individuals' interest in the videos is independent of the quality and adequacy of the videos. Ferhatoglu et al. (14) reported a negative correlation between video quality scores and video popularity. Celik et al. (6) reported that individuals were interested in insufficient information. We think that studies on the determinants of individuals' interest in medical videos are needed. It can be seen that attracting the attention of individuals is as important as providing accurate and complete information nowadays.

No correlation was found between the time from uploading the videos to their evaluation and the DISCERN and RCSS scores. When the videos were evaluated chronologically, no change in quality was seen. Considering the increasing interest in YouTube, we health professionals need to produce higher quality content.

This study has several limitations. First and foremost, only two search terms were used. Patients may be searching for different words, which may affect the results. As a non-Turkish phrase (like rotator kaf etc.), it is automatically corrected as "Rotator cuff" by the YouTube search engine, although it may be spelled differently by different

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individuals. Additionally, the search results and videos included are specific to the date of the search. Data on the Internet are continually changing and being updated. Finally, we are aware that searches using different IPs at different times may yield different results, depending on the daily changing trends and the algorithm used by the YouTube search engine. With today's techniques, data on the Internet in general and YouTube in, particular, cannot be evaluated in a holistic and precise manner with a single study.

CONCLUSION

With the current study, it was concluded that the Turkish videos on rotator cuff surgery accessed via the YouTube search engine were insufficient for informing patients. Orthopedic associations, physicians, and healthcare institutions should establish guidelines for the creation of informative documents and videos to be published for patients on the Internet and should check their quality and accuracy for the benefit of public health.

DECLARATIONS

Ethics Committee Approval
This study was exempt from ethical approval of the study institution because it involved the use of public access data only.

Conflict of Interests
The authors declare no conflict of interest.

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Informed Consent
Not needed.

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Did We Do It Right? The Effect of Postponing Elective Orthopedic Surgeries Due to the Pandemic on the Quality of Life

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ABSTRACT

Objective: To investigate the effect of the postponement of elective surgeries on the quality of life of the patients and to examine the post-operative COVID-19 rates of patients who underwent elective surgery and investigate the associated risk factors.

Methods: In this retrospective study, 187 patients who underwent elective surgery between June and July 2020 and between January and May 2021 were examined. Age, gender, occupation, comorbidity, time of surgical delay, type of surgery, hospitalization, and follow-up periods were recorded. Surgeries were categorized under four headings; knee arthroscopy, arthroplasty, rotator cuff repair/impingement, and minor surgery. To examine the quality of life of all operated patients, a validated Turkish version of EQ-5D-3L was used. All patients were questioned on phone to identify the risk factors for transmission. Statistical analyzes were performed using SPSS 26.0 version.

Results: Among the 187 patients evaluated in the study, 40 patients (21.4%) were diagnosed nCOV-19 during the postoperative period. Regardless of the type of surgery performed, mobility, pain/discomfort, and anxiety/depression scores were increased significantly postoperatively (p<0.05 for each). A significant relationship was found between younger age, surgery type, shorter hospitalization period, a greater number of visits to the outpatient clinic, longer follow-up period, history of nCOV-19 preoperatively, diagnosis of nCOV-19 among relatives and the diagnosis of nCOV-19 after surgery (p<0.05 for each).

Conclusion: By taking all possible precautions and avoiding identifiable risk factors, thus eliminating the risk of COVID-19 transmission as much as possible, and then performing elective surgeries will significantly increase the quality of life of the patients.

Keywords: COVID-19, nCOV-19, elective surgery, EQ-5D-3L, Quality of life, worse than death

Doğru Mu Yaptık? Pandemi Nedeniyle Elektif Ortopedik Ameliyatların Ertelenmesinin Yaşam Kalitesine Etkisi

ÖZET

Amaç: Elektif ameliyatların ertelenmesinin hastaların yaşam kalitesine etkisini araştırmak ve elektif cerrahi uygulanan hastaların ameliyat sonrası COVID-19 oranlarını ve ilişkili risk faktörlerini incelemek.

Yöntemler: Bu retrospektif çalışmada, Haziran-Temmuz 2020 ve Ocak-Mayıs 2021 tarihleri arasında elektif cerrahi uygulanan 187 hasta incelendi. Yaş, cinsiyet, meslek, komorbidite, cerrahi gecikme zamanı, cerrahinin türü, hastanede kalma ve takip süreleri kaydedildi. Ameliyatlar dört başlık altında toplandı; diz artroskopisi, artroplasti, rotator manşet tamiri/impingment ve minör cerrahiler. Ameliyat edilen hastaların yaşam kalitesini incelemek için, EQ-5D-3L'nin valide edilmiş Türkçe versiyonu kullanıldı. Tüm hastalar, risk faktörlerini belirlemek amacıyla telefonla arandı. İstatistiksel analizler SPSS 26.0 versiyonu kullanılarak yapıldı.

Bulgular: Çalışmada değerlendirilen 187 hastanın 40'ına (%21,4) ameliyat sonrası dönemde nCOV-19 tanısı konuldu. Yapılan ameliyatın türünden bağımsız olarak, hareketlilik, ağrı/rahatsızlık ve anksiyete/depresyon puanlarının ameliyat sonrası anlamlı olarak arttığı görüldü (her biri için p<0.05). Ameliyat sonrası nCOV-19 tanısı ile genç yaş, ameliyat tipi, kısa hastanede yatış süresi, fazla poliklinik ziyareti, uzun takip süresi, ameliyat öncesi nCOV-19 öyküsü ve akrabalarda nCOV-19 tanısı arasında anlamlı ilişki saptandı (her biri için p<0.05).

Sonuç: Olası tüm önlemleri alarak ve tanımlanabilir risk faktörlerinden kaçınarak, böylece COVID-19 bulaş riskini mümkün olduğunca azaltarak, elektif ameliyatların yapılması hastaların yaşam kalitesini önemli ölçüde artıracaktır.

Anahtar Kelimeler: COVID-19, nCOV-19, elektif cerrahi, EQ-5D-3L, Yaşam kalitesi, ölümden daha kötü

The coronavirus infection (nCOV-19), in which the first cases began to be seen towards the end of 2019, was declared as a pandemic on 11 March 2020 (1,2). This date is also the date when the first case was seen in our country (3). Especially in the early stages of the disease, preventive social measures have become very important due to the lack of definitive treatment and protective vaccines (4,5). In our country, in addition to many measures restricting social life, such as the prohibition of city entrances and curfews, serious restrictions have also been introduced in the hospitals.

One of the most important restrictions conducted in the hospitals was the suspension of all elective procedures between March and June 2020 (2). Moreover, even after the suspension has been removed, elective surgeries have been periodically stopped in our hospital between August 2020 and December 2020, so that all medical personnel and all available hospital beds could be allocated to the pandemics (6). On the other hand, many patients during this period applied to our hospital due to elective pathologies such as meniscal or anterior cruciate ligament (ACL) injuries, gonarthrosis, coxarthrosis, rotator cuff ruptures, ingrown nails, and carpal tunnel syndrome; and surgical treatment was suggested. However, in the light of current regulations, these surgeries had to be postponed to increase the number of medical staff and beds allocated to the pandemics and to protect the patients from the effects of the pandemic. On the other hand, it is an inevitable fact that these postponed surgeries reduce the quality of life of patients. Indeed, there are several studies in the literature stating that postponed surgeries reduce the quality of life and patients want to have elective surgery despite the risk of COVID-19 transmission (6-9).

Our primary objective in the study was to investigate the effect of the postponement of elective surgeries on the quality of life of the patients operated on in our clinic. Our secondary objective was to determine the postoperative nCOV-19 rates of patients who underwent elective surgery and to investigate the associated risk factors.

METHODS

Following the ethical board approval, all patients who were recommended surgical treatment during the period when elective surgeries were suspended (March-June 2020 and August-December 2020) and who underwent elective surgery after the suspension was lifted (June-July 2020 and January-May 2021) were examined retrospectively. Patients who underwent emergency and/or trauma

surgeries, patients who were not recommended for surgery at the time of the restrictions, patients who had surgery in different hospitals, patients who are healthcare workers, and patients who did not agree to participate in the study or whose follow-up information could not be reached were excluded from the study. Considering all the inclusion and exclusion criteria, 187 patients were evaluated.

Age, gender, occupation, comorbidity, time of surgical delay, type of surgery, hospitalization, and follow-up periods of all patients were recorded from the patient files. Occupations were grouped under three headings according to the need for movement; not working/retired, less active occupation (civil servant, accountant), or highly active occupation (security guard, furniture maker). In terms of comorbidity, only systemic diseases requiring drug use were accepted as comorbidities (such as hypertension or diabetes mellitus). Surgeries were categorized under four headings; Knee Arthroscopy (diagnostic knee arthroscopy, meniscal injury repair, ACL reconstruction), Arthroplasty (total knee arthroplasty, total hip arthroplasty, revision knee arthroplasty), Rotator Cuff Repair/Impingement (open repair, acromioplasty), and Minor Surgery (implant removals and all kinds of procedures performed under local anesthesia such as nail bed revision, nervus medianus decompression, and trigger finger surgery).

All patients were called in November 2021 from the phone numbers recorded in their files to question whether they were diagnosed with nCOV-19 after the surgery, the risk factors for transmission, and the quality of life before and after the surgery. While the delay time of the surgery was determined as the number of days between the date of the first outpatient clinic control when the surgery was recommended to the patient and the date of the surgery; postoperative follow-up period was determined as the number of days between the day of the surgery and the date the patient was called in November 2021.

To examine the quality of life of all operated patients, a validated Turkish version of EQ-5D-3L (registration number: 40403) was acquired from the EuroQol website (10,11). In this official survey, patients' quality of life was questioned under 6 headings; mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and visual pain scale (VPS). The first three headings (mobility, self-care, and usual activities) were evaluated with 3 answers (no problem was categorized under "1"; little discomfort was categorized under "2" and unable to do was categorized under "3") whereas fourth and fifth headings (pain/discomfort and anxiety/depression) were again evaluated

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with 3 answers (no problem was categorized under "1"; moderate pain or anxiety were categorized under "2" and extreme pain or anxiety were categorized under "3"). In the last heading (VPS), the patients were asked to give a score of 0-100 for their pain, with 0 being unbearable resting pain and 100 being a pain-free normal life. All patients were asked to fill out the survey twice, taking into account their pre-operative situation in one and their current situation in the other, thus by evaluating the effect of the surgery on the quality of life of the patients, it can be interpreted whether the delay of the surgery reduced the quality of life.

To examine the post-operative nCOV-19 rates of patients who underwent elective surgeries and to determine the associated risk factors; when the patients were called, the number of visits to the outpatient clinics related to surgery, whether they had a history of nCOV-19 before or after surgery, whether they had relatives diagnosed with nCOV-19, whether they traveled between cities, and whether they were staying in the same house with any healthcare worker was questioned and the answers were recorded. Patients were divided into two subgroups according to whether they were diagnosed with nCOV-19 between the date of surgery and November 2021, and all responses were analyzed accordingly; Group 1 consisted of patients who were not diagnosed with nCOV-19, and Group 2 consisted of patients diagnosed with nCOV-19 (Table 1).

Statistical analyzes were performed using SPSS 26.0 version. Mean (minimum-maximum) values and frequency (percentile) were used as descriptive statistics. The compliance of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Student T-Test was used for normally distributed variables whereas Mann Whitney U and Wilcoxon Signed Ranks Tests were used for non-normally distributed variables. Comparison of categorical data has been conducted with the Chi-Square Test, and for data that does not meet the Chi-Square conditions, Fischer's exact test was used. The cases where the p-value was less than 0.05 were considered statistically significant.

RESULTS

Among the 187 patients evaluated in the study, 40 patients (21.4%) were diagnosed nCOV-19 during the postoperative period. While 82 patients (43.8%) had undergone knee arthroscopy surgeries, 51 patients (27.3%) had joint replacements, 14 patients (7.5%) had rotator cuff tear repairs and/or acromioplasty and 40 patients (21.4%) had minor surgeries. A significant relationship was found between younger age, surgery type, shorter hospitalization period, a greater number of visits to the outpatient clinic, longer follow-up period, history of nCOV-19 preoperatively, diagnosis of nCOV-19 among relatives, and the diagnosis of nCOV-19 after surgery (p<0.05 for each). Detailed demographic profile of the patients, COVID-19 transmission rate, and all related factors can be seen in Table 1.

The average delay time of elective surgeries performed in our clinic was 78.48 days (Range: 3 – 540 days). Regardless of the type of surgery performed, mobility, pain/discomfort, anxiety/depression, and VPS scores of all patients were increased significantly postoperatively (p<0.05 for each). Furthermore, self-care scores of Knee Arthroscopy and Rotator Cuff Repair/Impingement groups were increased significantly (p=0.046 and p=0.001, respectively) On the other hand, only in the Minor Surgery group, a significant decrease was observed in the usual activities score (p=0.014). The change in the quality of life of the patients postoperatively based on the type of surgery performed can be seen in Table 2.

DISCUSSION

During the pandemic of our age, elective surgeries have been ceased in most countries to reduce hospital admissions and to direct facilities to pandemic patients (6,8,9,12-14). In orthopedics, especially patients who are waiting for knee and hip arthroplasties are affected by this situation, and they are forced to live with a very low quality of life, which is described as "worse than death" situation in the literature (7,8). On the other hand, knee and hip arthroplasties are not the only elective surgeries in orthopedics, and also knee and hip arthritis are not the only pathologies that reduce the quality of life. As far as we know, this is one of the first studies investigating the effects of postponing all orthopedic elective surgeries on quality of life on such a large scale. This constitutes the main strength of our study. The most important finding of our study is the significant increase in the postoperative quality of life of patients whose surgery was postponed, regardless of the surgery type. To be specific; mobility, pain/discomfort, anxiety/depression, and VPS scores of all surgery types were increased significantly (p<0.05 for each). The negative impact of postponing elective surgeries due to COVID-19 on quality of life, which is our main hypothesis, emerges at this point; Surgeries postponed due to the pandemic mean that this increase in quality of life is delayed and the patient continues to live with a low quality of life during the postponement period. Furthermore, in terms of postoperative nCOV-19 rates, several associated risk factors such as younger age, shorter hospitalization period, a greater number of visits to the outpatient clinics, history of nCOV-19 preoperatively, and diagnosis of nCOV-19 among relatives have been identified (p<0.05 for each).

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Table 1: Subgroup analysis regarding the associated risk factors in the development of nCOV-19 after elective surgeries		Group 1 (N=147)	Group 2 (N=40)	Total (N=187)	p
Age (years)		51.35 (17 – 81)	40.8 (23 – 60)	49.09 (17 – 81)	**<0.001**
Gender	Male	58 (39.5%)	20 (50%)	78 (41.7%)	0.230
	Female	89 (60.5%)	20 (50%)	109 (58.3%)	
Occupation	Not working	13 (8.8%)	8 (20%)	21 (11.2%)	0.058
	Less active	100 (68%)	20 (50%)	120 (64.2%)	
	Highly active	34 (23.2%)	12 (30%)	46 (24.6%)	
Comorbidity	No	92 (62.6%)	28 (70%)	120 (64.2%)	0.386
	Yes	55 (37.4%)	12 (30%)	67 (35.8%)	
Surgery Type	Arthroscopy	58 (39.5%)	24 (60%)	82 (43.8%)	**0.003**
	Arthroplasty	47 (32%)	4 (10%)	51 (27.3%)	
	RCR/I	14 (9.5%)	0	14 (7.5%)	
	Minor Surg	28 (19%)	12 (30%)	40 (21.4%)	
Hospitalization Period (days)		3.51 (0 – 11)	2.15 (0 – 10)	3.22 (0 – 11)	**0.001**
Number of Visits to the Outpatient Clinic		1.99 (0 – 10)	2.35 (0 – 6)	1.64 (0 – 10)	**0.030**
Follow-up after Surgery (days)		283.45 (214 – 523)	335.55 (205 – 523)	294.59 (205 – 523)	**<0.001**
History of nCOV-19 Preoperatively	No	137 (93.2%)	30 (75%)	167 (89.3%)	**0.003**
	Yes	10 (6.8%)	10 (25%)	20 (10.7%)	
Diagnosis of nCOV-19 among Relatives	No	73 (49.7%)	10 (25%)	83 (44.4%)	**0.005**
	Yes	74 (50.3%)	30 (75%)	104 (55.6%)	
Travel History After Surgery	No	63 (42.9%)	22 (55%)	85 (45.5%)	0.171
	Yes	84 (57.1%)	18 (45%)	102 (54.5%)	
Healthcare Worker Relative	No	86 (58.5%)	22 (55%)	108 (57.8%)	0.691
		61 (41.5%)	18 (45%)	79 (42.2%)	

Mean (Minimum – Maximum) values were used for numerical data whereas frequency (percentile) was used for categorical data; N: number of patients; P: statistical significance value; RCR/I: shoulder impingment and/or rotator cuff tear related operations; Minor Surg: all operations conducted under local anesthesia and implant removals

One of the most important reasons for the postponement of elective surgeries is the desire to reduce the patient load in hospitals (6,15). After all, a patient comes to the outpatient clinics for follow-ups more than once after elective surgery. Indeed, a significant relationship was found between a greater number of visits to the outpatient clinics and postoperative nCOV-19 rates in our study (p=0.030). On the other hand, a significant relationship was found between younger age, shorter hospitalization period, and nCOV-19 rates in our study (p<0.001 and p=0.001, respectively). A significant relationship was also found between surgery type and nCOV-19 rates (p=0.003); nCOV-19 rates were found to be higher in patients who underwent knee arthroscopy and minor surgeries. These findings differ from the literature. Clement et al. have reported a postoperative nCOV-19 rate of 1%, with the only significant risk factor being longer hospitalization period (12). Yapp et al.

have stated that a longer hospitalization period is associated with positive COVID-19 status (16). On the other hand, in our study, the postoperative nCOV-19 rate was found to be 21.4% and a shorter hospitalization period was found to be an important risk factor (p<0.001). The patient population undergoing knee arthroscopy and minor surgery generally consists of younger patients, and the hospitalization period of these patients is shorter while older patients usually undergo arthroplasty surgeries that may require longer hospitalization. Considering the dangerous course of nCOV-19 in the elderly, older patients are much more cautious, especially in terms of post-operative transmission; On the other hand, the more careless behavior of younger patients may explain the higher nCOV-19 rates in patients who underwent arthroscopy and minor surgeries and had a shorter hospital stay.

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Table 2: Variation of patients' pre- and post-operative quality of life			Arthroscopy (N=82)	Arthroplasty (N=51)	RCR/I (N=14)	Minor Surg (N=40)
Follow-up After Surgery (days)			287.77 (205 – 523)	306.08 (214 – 523)	309.36 (228 – 499)	288.77 (206 – 492)
Time of Surgical Delay (days)			103.32 (10 – 540)	47.35 (3 – 240)	62 (4 – 180)	73 (5 – 210)
Mobility	Pre	1	6 (7.3%)	0	6 (42.9%)	26 (65%)
		2	74 (90.2%)	51 (100%)	6 (42.9%)	14 (35%)
		3	2 (2.4%)	0	2 (14.3%)	0
	Post	1	38 (46.3%)	35 (68.6%)	10 (71.4%)	30 (75%)
		2	42 (51.2%)	16 (31.4%)	4 (28.6%)	10 (25%)
		3	2 (2.4%)	0	0	0
	p		<0.001	<0.001	0.014	0.046
Self-Care	Pre	1	74 (90.2%)	33 (64.7%)	0	40 (100%)
		2	8 (9.8%)	18 (35.3%)	14 (100%)	0
		3	0	0	0	0
	Post	1	78 (95.1)	35 (68.6%)	12 (85.7%)	38 (95%)
		2	4 (4.9%)	10 (19.6%)	2 (14.3%)	2 (5%)
		3	0	6 (11.8%)	0	0
	p		0.046	0.157	0.001	0.157
Usual Activities	Pre	1	70 (85.4%)	33 (64.7%)	10 (71.4%)	36 (90%)
		2	12 (14.6%)	18 (35.3%)	4 (28.6%)	4 (10%)
		3	0	0	0	0
	Post	1	70 (85.4%)	37 (72.5%)	12 (85.7%)	30 (75%)
		2	12 (14.6%)	12 (23.5%)	2 (14.3%)	10 (25%)
		3	0	2 (3.9%)	0	0
	p		1.000	0.414	0.157	0.014
Pain Discomfort	Pre	1	8 (9.8%)	2 (3.9%)	0	8 (20%)
		2	52 (63.4%)	22 (43.1%)	12 (85.7%)	28 (70%)
		3	22 (26.8%)	27 (52.9%)	2 (14.3%)	4 (10%)
	Post	1	30 (36.6%)	20 (39.2%)	6 (42.9%)	22 (55%)
		2	42 (51.2%)	24 (47.1%)	8 (57.1%)	12 (30%)
		3	10 (12.2%)	7 (13.7%)	0	6 (15%)
	p		<0.001	<0.001	0.005	0.003
Anxiety Depression	Pre	1	20 (24.4%)	12 (23.5%)	4 (28.6%)	10 (25%)
		2	22 (26.8%)	29 (56.9%)	4 (28.6%)	20 (50%)
		3	40 (48.8%)	10 (19.6%)	6 (42.9%)	10 (25%)
	Post	1	34 (41.5)	34 (66.7%)	8 (57.1%)	24 (60%)
		2	20 (24.4%)	9 (17.6%)	2 (14.3%)	8 (20%)
		3	28 (34.1%)	8 (15.7%)	4 (28.6%)	8 (20%)
	p		<0.001	<0.001	0.014	<0.001
VPS	Pre		51.46 (10 – 90)	48.04 (30 – 70)	44.29 (30 – 50)	60.5 (10 – 80)
	Post		73.17 (10 – 90)	75.49 (40 – 100)	80 (50 – 100)	73 (10 – 100)
	p		<0.001	<0.001	<0.001	<0.001

Mean (Minimum – Maximum) values were used for numerical data whereas frequency (percentile) was used for categorical data; N: number of patients; P: statistical significance value; RCR/I: shoulder impingement and/or rotator cuff tear related operations; Minor Surg: all operations conducted under local anesthesia and implant removals; Pre: Preoperatively; Post: Postoperatively.

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Although nCOV-19 re-infections can occur, this is not very common due to the nature of the viral infection (17). Indeed, in our study, patients with no preoperative history of nCOV-19 had higher rates of postoperative disease (p=0.003). On the other hand, the significant relationship between nCOV-19 diagnosis among relatives and postoperative infection rates (p=0.005) can be explained by the "get well soon" visits, which are common despite the pandemic, due to the sociocultural structure of our society. It is important to keep in mind that, compared to the nCOV-19 rates after elective surgeries in the literature, our infection rate is much higher (21.4%). The reason for this is that the studies in the literature generally consider the diagnosis of infection in the early postoperative period (12,16,18) whereas, in our study, postoperative nCOV-19 rates were evaluated after an average of 294.59 days (range: 205-523 days) of follow-up. It is not possible to consider all high-risk actions of patients during this period and to determine all risk factors accordingly. The fact that the mean postoperative follow-up period of the patient group diagnosed with nCOV-19 postoperatively was longer (p<0.001) also supports this hypothesis. After all, the nCOV-19 rates increase as the patients' follow-up period increases.

The primary purpose of elective surgeries, which are usually indicated following chronic processes, is almost always to increase the quality of life (19). Indeed, in our study, a significant increase was found in the quality of life of all our patients after elective surgery (p<0.05 for each). Postponed arthroplasty surgeries are a subject of particular interest in the literature. Clement et al. have stated that patients who have delayed knee or hip replacement surgery are defined as "worse than death" and over 80% of the patients have reduced quality of life due to postponement of elective surgeries (8). Madanipour et al. have reported that over 70% of the patients wished to proceed with surgery, regardless of the virus transmission risk (9). In our study, the patients' mobility, pain/discomfort, anxiety/depression, and VPS scores increased significantly after arthroplasty operations performed following an average delay of 47.35 days (range: 3-240 days) (p<0.001 for each). An important detail to highlight here is that the longest delay period is 240 days. It should be kept in mind that patients who are in a "worse-than-death" state and all patients who do not want to wait until the postponement of elective surgeries are over had elective surgeries in centers other than our hospital and were not included in our study. Different results can be obtained with multicenter studies including these patients.

Postoperative mobility, self-care, pain/discomfort, anxiety/depression, and VPS scores increased significantly in patients who underwent knee arthroscopy, with a mean delay of 103.32 days (range: 10-540 days) (p<0.001, p=0.046, p<0.001, p<0.001, and p<0.001, respectively). Similarly, mobility, self-care, pain/discomfort, anxiety/depression, and VPS scores increased significantly in patients who underwent open surgery for rotator cuff repair and/or impingement, with an average waiting time of 62 days (range: 4-180 days) (p=0.014, p=0.001, p=0.005, p<0.001 and p<0.001, respectively). On the other hand, while the quality-of-life scales showed similar changes in the minor surgery group with an average delay time of 73 days (range: 5-210 days); the usual activities score decreased postoperatively (p=0.014). Although we could not be able to explain the decrease in the usual activities score while there was an increase in other quality of life scores, we believe that the fact that these surgeries had to be performed as quickly as possible under local anesthesia may have affected the results.

There are several limitations in our study. First and foremost, although our limited phone call evaluated several parameters; there are too many confounding factors regarding COVID-19 transmissions, such as using masks, social distancing, going to hospitals, or any other high-risk areas for any reason. Moreover, it was not questioned in our study whether the patients received post-operative physical therapy, and if they did, whether they received it at home or in a physical therapy center. Admitting it is very difficult, risk factors for postoperative transmission can be revealed more clearly with comprehensive studies in which all relevant parameters are evaluated. Secondly, although it is easy to use, practical, and supported by the literature, the EQ-5D-3L questionnaire is not the only scoring system that measures patients' quality of life. Different results can be obtained with different and comprehensive scoring systems. Thirdly, as described in the methods section, patients were called in November 2021 and asked to fill out the questionnaire twice, one is for pre-operative and the other for post-operative assessments. Since patients are prone to forget the degree of pain they felt before surgery, they may give biased scores for historical pains and this is an important limitation. Finally, as mentioned before, we have only included patients that were operated on in our hospital. Thus, patients who could not wait, in other words, "worse than death" patients, were not included in the study. More clear results can be obtained with multicenter, comprehensive studies.

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CONCLUSION

In conclusion, although elective surgeries have to be ceased from time to time to protect patients and cope with the increasing patient burden during the pandemic of our age, these postponements have dramatic effects on patients' quality of life. Taking all possible precautions, and avoiding identifiable risk factors, thus eliminating the risk of virus transmission as much as possible and then performing elective surgeries will significantly increase the quality of life of the patients.

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Conflicts of Interest
The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Ethical Approval
This study was approved by the Ministry of Health and the local ethics committee.

Consent to Participate
Informed consent was obtained from all individual participants included in the study.

Consent to Publish
All authors agreed with the content and all authors gave explicit consent to submit the study. Authors have obtained consent from Ministry of Health and Ankara City Hospital. Patients signed informed consent regarding publishing their data.

Availability of Data and Materials
All data have deposited in a repository.

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The Efficacy of Low-Dose Enoxaparin in Psoriasis

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ABSTRACT

Psoriasis is a frequently encountered inflammatory skin disease with unclear etiology and no curative therapy. Enoxaparin is a low-molecular weight heparin analogue. Heparin and its analogues in low doses have antiproliferative and immunomodulatory effects. Low-dose enoxaparin has inhibitory effects on T cell-mediated immune reactions. T lymphocytes play a key role in the immunopathogenesis of psoriasis. The aim of this study was to evaluate the efficacy of low-dose enoxaparin in the treatment of psoriasis. Twenty-three patients with chronic plaque and guttate psoriasis were enrolled in an open study. Patients were given subcutaneous injections of 5 mg enoxaparin once weekly for a total of 6 weeks. There was a statistically significant difference between the PASI (Psoriasis Area and Severity Index) scores at the beginning and at the 6th week follow up (p=0.008). Four out of 23 patients (17%) showed marked improvement (≥50% reduction in PASI score), 8 patients (35%) showed moderate improvement (25-49% reduction in PASI score), 5 patients (22%) were unchanged (<25% reduction in PASI score). Six patients (26%) experienced worsening with a corresponding increase in the PASI scores. Based on these findings, 52% of patients were considered to get benefit from enoxaparin treatment. No systemic side-effects due to enoxaparin were observed. The only local side-effect recorded in 7 patients (30%) was ecchymosis at the injection site. Low-dose enoxaparin, which appears to be safe, is a candidate to become a future alternative in the treatment of psoriasis. Further studies assessing the optimum dose and duration of treatment, as well as patient subgroups that will benefit most from enoxaparin treatment are warranted. In addition, efficacy of enoxaparin in psoriasis should be compared to those of standard therapeutic modalities.

Keywords: Enoxaparin, psoriasis, treatment, low-molecular-weight heparin

Psoriazis Hastalarinda Düşük Doz Enoksaparinin Etkinliği

ÖZET

Psoriazis sık görülen, etyolojisi aydınlatılmamış ve kesin tedavisi olmayan inflamatuvar bir deri hastalığıdır. Enoksaparin düşük moleküler ağırlıklı bir heparin türevidir. Heparin ve türevleri düşük dozlarda antiproliferatif ve immünomodülatör etkilere sahiptir. Düşük doz enoksaparin özellikle T hücre aracılı immün reaksiyonları bloke etmektedir. T lenfositler psoriazis immünpatogenezinde temel rol oynayan hücrelerdir. Bu çalışmanın amacı, düşük doz enoksaparinin psoriazis tedavisindeki etkinliğini araştırmaktı. Bu amaçla, tek merkezli, tek kollu ve prospektif bir çalışma planlandı. Kronik plak ve guttat tip psoriazisli toplam 23 hastaya, haftada 1 kez, 5 mg emoksaparin subkutan enjeksiyon şeklinde uygulandı. Hastaların başlangıç PASI (Psoriazis Alan ve Şiddet İndeksi) skorları ile 6 haftalık tedavi sonundaki PASI skorları arasında istatistiksel olarak anlamlı fark saptandı (p=0,008). Dört hastada (%17) belirgin düzelme (PASI skoru azalması ≥ %50), 8 hastada (%35) orta dereceli düzelme (PASI skoru azalması %25-49) izlendi. Beş hastada (%22) PASI skorundaki azalma %25'ten az idi. Altı hastada (%26) ise PASI skorunda başlangıca göre artış mevcuttu. Bu bulgulara göre hastaların %52'sinde PASI skorundaki azalma anlamlı idi. Hiçbir hastada enoksaparine bağlı sistemik yan etki gözlenmedi. Tek lokal yan etki, 7 hastada (%30) enjeksiyon bölgesinde ekimoz oluşumu idi. Düşük doz enoksaparin, güvenli yan etki profiliyle psoriazis tedavisinde alternatif bir tedavi seçeneğidir. Etkinlik açısından ise, enoksaparinin psoriazisde uygun doz ve kullanım süresinin, hedef hasta alt grubunun belirlenmesine ve standart psoriazis tedavileri ile karşılaştırılmasına yönelik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Enoksaparin, psoriazis, tedavi, düşük moleküler ağırlıklı heparin

Psoriasis is a frequently encountered, chronic inflammatory skin disease. The etiopathogenesis of the disease remains unclear. Clinical presentation and severity of psoriasis may vary in different patients and during different life periods in the same patient. Although not considered a mortal disease, psoriasis has a great negative impact on the affected patients' quality of life, because it creates psychological stress, feelings of shame and physical discomfort.

Current modalities of treatment consist of topical agents, phototherapy, and systemic medications; however, none of these options offers a cure for the disease. Routinely available systemic treatment alternatives have potential serious side effects, which limit their long-term use in a lifetime chronic disease. Research continues to elucidate safer systemic treatment methods with fewer side effects.

The two main events in the pathogenesis of psoriasis are keratinocyte hyperproliferation and dermal inflammation. In recent years, the pivotal role of cellular immune system, especially T lymphocytes, in the immunopathogenesis of psoriasis has been firmly established (1,2). In the light of this information, novel therapeutics with immunomodulatory effects have been developed (3).

Enoxaparin is a low molecular weight (LMW) heparin derivative. It is widely used as an anticoagulant in the prophylaxis and treatment of venous thrombosis. Studies have shown that heparin has immunomodulatory effects at low doses, where it cannot exert an anticoagulant effect. It can inhibit T lymphocyte-mediated reactions, especially due to its negative effects on T lymphocytes (4-6). Heparin and its derivatives also have suppressive effects on keratinocyte proliferation (7). It has recently been reported that low-dose enoxaparin is effective in the treatment of lichen planus, a T-cell-mediated dermatosis (8,9).

The present study aimed to assess the possible clinical efficacy of low-dose enoxaparin in the treatment of psoriasis, grounded on encouraging results from previous studies and considering the fundamental role of T cells in the pathogenesis of psoriasis.

PATIENTS AND METHODS

Patients who applied to Hacettepe University School of Medicine Department of Dermatology Clinic between March 2001 and August 2001 and diagnosed with psoriasis were recruited in this study. The study was planned as a single-center, single-arm, and prospective study.

Inclusion Criteria

Patients with psoriasis, who met the following criteria were enrolled:

1. Age 18 and above

2. Diagnosis of plaque or guttate type psoriasis

3. Involvement of more than 20% of the body surface

4. Diagnosis of psoriasis confirmed by biopsy and histopathological examination

5. No systemic (oral, parenteral, photobiological) treatment for psoriasis within the last 3 months

6. No topical treatment for psoriasis within the last month

7. Patient approval to participate in the study and signing the "Patient Consent Form"

Exclusion Criteria

Patients with psoriasis, who met the following criteria were excluded:

1. Pregnancy or lactation

2. History of bleeding diathesis, uncontrolled hypertension, cerebrovascular accident, peptic ulcer

3. Hypersensitivity to heparin and heparin derivatives and a history of heparin-induced thrombocytopenia

4. History of major surgery within the last 3 months

5. Having a family history of bleeding diathesis, or cerebrovascular accident

6. Concomitant use of oral anticoagulants, acetylsalicylic acid, or other nonsteroidal anti-inflammatory drugs

7. Liver disease and/or abnormal liver function tests

8. Abnormal kidney function tests.

Study Plan

Before starting the treatment, each patient's age, gender, duration of the disease, the presence of psoriasis in the family, and previous treatment methods were questioned and recorded in the pre-prepared forms. Detailed systemic inquiry, particularly questioning of the exclusion criteria, systemic physical and dermatological examination were performed. The clinical type of psoriasis was determined and recorded.

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Before the treatment, the extent and severity of the disease were calculated by two different observers using the PASI (Psoriasis Area and Severity Index) scoring method, and the mean of the two values was accepted as the initial PASI score. The patients' lesions were marked on a diagram representing the human body and photographed. Before treatment, laboratory tests including complete blood count, liver and kidney function tests, prothrombin time and active partial thromboplastin time were ordered in all patients.

To avoid possible drug interactions, patients were warned not to use any medications (including painkillers) concurrently without the knowledge of the physician. Also, they were not allowed to use any concomitant topical agents (including moisturizers) during the period of enoxaparin therapy.

During treatment, patients received 5 mg enoxaparin (Clexane®; Eczacıbaşı-Rhone-Poulenc) as a subcutaneous injection once a week for 6 weeks. A 5 mg injection dose was prepared as 0.05 ml in a 26 Gauge insulin syringe, drawn from 20 mg/0.2 ml commercial enoxaparin preparation.

The abdomen was used as the subcutaneous injection site. The injection was administered to the abdominal wall, approximately 10 cm lateral to the midline. The site of injection was alternated every week, i.e., if one dose was given to the right side, the other was administered to the left.

Before each injection, patients were questioned for possible local and systemic side effects. Physical examination and local examination of the previous injection site were performed. Complete blood count and activated partial thromboplastin time were ordered weekly; liver function tests were repeated at the end of the treatment (after the 6th dose). Three weeks and 6 weeks after the start of treatment, PASI scores were calculated by two different observers and the average of the values was recorded. At the end of the treatment, the patients were photographed again.

Evaluation Criteria

Pre-treatment psoriasis area (involved body parts) and severity and response to treatment of the patients in the study group were evaluated using the PASI scoring system (10). In this scoring system, the area is determined by dividing the body into 4 main regions: head, upper extremities, trunk, and lower extremities. These regions were considered to constitute 10%, 20%, 30% and 40% of the total body surface, respectively. For each of the four regions, the area affected by psoriasis was scored with a number value between 0 and 6 according to the percentage of surface area involved. For each site, erythema (E), induration (I), and desquamation (D) were seperately evaluated with a score range of 0-4.

Response to enoxaparin treatment was determined according to changes in PASI scores. After 6 weeks of enoxaparin treatment, 50% or more reduction in PASI score was accepted as "significant improvement", and a decrease of 25-49% was considered as "moderate improvement". Significant and moderate improvement outcomes were accepted as positive responses to enoxaparin. Less than 25% reduction in PASI score was evaluated as "no significant change".

Statistics

Due to limited number of patients in the study group and the non-normal distribution of PASI scores, Wilcoxon test, which is a non-parametric method, was used to compare the PASI values of patients before and after the 6th week of treatment. The Mann-Whitney U test, which is also a non-parametric test, was used to investigate the relationship between the presence of a family history and the age of onset of psoriasis. In comparison of other parameters, cross tables were created and the difference between the groups was tested with the chi-square method.

All statistical evaluations were made using SPSS (Statistical Packages for Social Sciences) for MS Windows Release 10.0.

RESULTS

Twenty-three patients with chronic plaque and guttate psoriasis, 13 males and 10 females, completed the study. The mean age of the patients participating in the study was 36 ± 11 years. The youngest patient was 19 years old, and the oldest patient was 57 years old. The age of onset of the disease ranged from 6 to 38 years, with a mean age of onset of 23 ± 8 years. The mean disease duration was 12.8 ± 9.6 years, and the median disease duration was 12 years (range 0-35 years). The shortest duration of disease was 1 month. Family history of psoriasis was positive in 16 patients (70%) and negative in 7 patients (30%). The age of onset was statistically significantly different in patients with a positive and negative family history (p=0.048). Family history was positive in all 5 patients whose age at onset was 15 years or younger. Demographic characteristics and treatment outcome in enrolled patients are summarized in Table 1.

#	G	A	AD	D	F	Ty	PrTx	PASI$_0$	PASI$_6$	PASI$_c$	CR
1	M	52	22	30	+	Pl	T, PUVA, UVB, C, R, M	19.0	23.6	24% ↑	Wor
2	M	35	25	10	+	Pl	T, UVB	24.6	18.0	27% ↓	Moderate
3	M	29	9	20	+	Pl	T, PUVA, M	18.9	16.3	14% ↓	NC
4	M	45	30	15	-	Pl	T, M	11.8	7.0	41% ↓	Moderate
5	M	44	21	23	+	Pl	T, PUVA	29.7	20.1	32% ↓	Moderate
6	M	41	29	12	+	Pl	T	22.2	21.4	4% ↓	NC
7	F	45	21	24	+	Gu	T, PUVA, UVB	18.3	20.1	9% ↑	Wor
8	F	23	6	17	+	Gu	T, UVB	8.8	3.6	59% ↓	Significant
9	M	19	15	4	+	Pl	T	12.3	11.5	7% ↓	NC
10	M	20	14	6	+	Pl	T, PUVA, UVB, C	29.7	32.2	8% ↑	Wor
11	M	40	31	9	+	Pl	T, PUVA, UVB, C, R	25.0	30.2	21% ↑	Wor
12	F	57	22	35	-	Pl	T, PUVA, UVB, C, R M	15.2	8.9	41% ↓	Moderate
13	M	26	20	6	-	Gu	T	20.8	13.5	35% ↓	Moderate
14	F	46	33	13	-	Pl	T, M	28.2	15.3	46% ↓	Moderate
15	F	22	19	3	+	Pl	T	11.7	7.3	38% ↓	Moderate
16	F	44	28	16	-	Pl	T, C, SS	26.1	22.1	15% ↓	NC
17	M	19	14	5	+	Pl	T, UVB	16.0	11.2	30% ↓	Moderate
18	F	41	29	12	+	Pl	T	16.2	15.6	4% ↓	NC
19	M	44	19	25	+	Pl	T, UVB	13.5	14.5	7% ↑	Wor
20	F	37	34	3	+	Pl	T	25.4	30.2	19% ↑	Wor
21	F	38	38	0.08	-	Gu	T	15.2	0	100% ↓	Moderate
22	F	28	24	4	+	Gu	T	12.0	2.8	77% ↓	Moderate
23	M	29	26	3	-	Gu	T, SS	43.2	18.3	58% ↓	Moderate

Abbreviations: **#**: Patient no.; **G**: gender (**M**: male; **F**: female); **A**: age; **AD**: age at diagnosis; **D**: duration (years); **F**: family history; **Ty**: Type of psoriasis (**Pl**: Plaque versus **Gu**: Guttate); **PrTx**: Previous therapies (**T**: topical corticosteroids and/ or calcipotriol; **C**: cyclosporine; **R**: oral retinoid; **M**: Methotrexate; **SS**: systemic steroids); **PASI$_0$**: PASI score at baseline; **PASI$_6$**: PASI score at the end of treatment; **PASI$_c$**: Change in PASI score (percent) with enoxaparin; **CR**: clinical response (**Wor**: worsening; **Moderate**: moderate response; **Significant**: significant response; **NC**: no change).

The mean pre-treatment PASI score of patients was 20.2 ± 8.0 (range 8.8 to 43.2). After the 6th dose of enoxaparin treatment, the mean post-treatment PASI score was 15.81 ± 8.73. There was a statistically significant difference between the initial and final PASI scores (p=0.008).

A reduction in PASI scores was detected at the end of the treatment in 17 (74%) of 23 patients included in the study: significant improvement in 4 patients (17%); and moderate improvement in 8 patients (35%). In five patients (22%), there was no significant change in PASI scores. Six patients (26%) had an increase in PASI scores ranging from 7.4% to 24% at the end of treatment compared to baseline values. The outcome of enoxaparin therapy according to the changes in PASI scores, is shown in Figure 1. Photographs of two demonstrative patients, before and after the 6th dose of enoxaparin, are shown in Figures 2-5.

In 3 of 17 patients who had a decrease in PASI score after the sixth dose of injection, there was initially an increase in the PASI score of 5-7.5% compared to the baseline after the third dose. The decrease in PASI scores after the sixth dose was less than 25% in all 3 patients.

There was no significant correlation between the change (decrease or increase) in the PASI score at the end of the treatment and gender, age of onset of the disease, duration of the disease, clinical form of psoriasis and previous treatments for psoriasis (p>0.05). A statistically significant correlation was found between family history and the change in PASI score (p=0.06). Family history was positive in all 6 patients whose PASI scores were increased at the end of the treatment.

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Outcome of therapy in patients
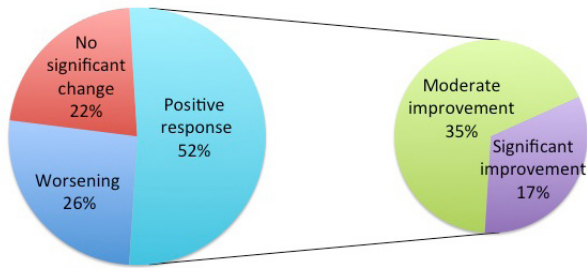
Figure 1. Outcome with enoxaparin treatment in patients with psoriasis. Positive response: PASI score reduction ≥25% (significant improvement: PASI score reduction ≥50%, moderate improvement: PASI score reduction 25-49%). Negative response: no significant change: PASI score reduction <25%.

Figure 4. Another demonstrative patient with psoriasis before enoxaparin treatment.

Figure 2. A demonstrative patient with psoriasis before enoxaparin treatment.
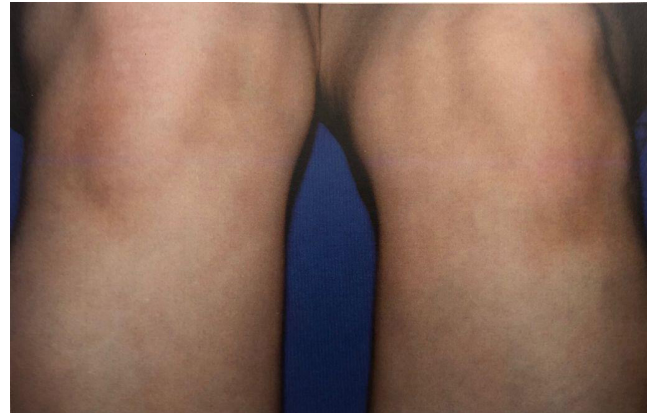
Figure 5. Patient in Figure 4 after enoxaparin treatment.

Figure 3. Patient in Figure 2 after enoxaparin treatment.

Weekly complete blood count and activated partial thromboplastin time during the treatment and liver function tests repeated at the end of the treatment were within normal limits in all patients. No systemic side effects or complications related to enoxaparin that required discontinuation of treatment were observed in any of the patients. Ecchymosis formation at the injection site, as the only local side effect related to treatment, was observed in 7 patients (30%). The ecchymoses spontaneously regressed within 2 weeks in all patients.

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DISCUSSION

Psoriasis is a common, chronic autoinflammatory and autoimmune disease, that especially affects young adults. Currently, there is no treatment method that provides a complete cure for the disease. Therefore, there is a need for novel, systemic, more effective, and safer therapeutics, appropriate for long-term use.

In the past, the target of systemic treatments for psoriasis has been hyperproliferative keratinocytes. Today, it is known that many of the traditional systemic treatment methods not only harbor antimitotic effects, but immunosuppressive and immunomodulatory effects as well. Immunological studies conducted in recent years have revealed the importance of T-lymphocyte-mediated immunological reactions in the development of psoriasis. Activated T lymphocytes in psoriatic lesions secrete heparin-binding epidermal growth factor (EGF)-like growth factor, which causes epidermal hyperplasia, in conjunction with T helper cell type-1 and type-2 cytokines (11,12).

Activated T lymphocytes harbor a heparinase enzyme, that assists these cells in crossing vascular barriers, entering the extracellular matrix, and reaching their target tissues. This enzyme can degrade heparin sulfate side chains of extracellular matrix proteoglycans (13,14). Lider et al. (5), has shown that low-dose heparin suppresses T lymphocyte heparinase activity and simultaneously inhibits T cell migration and delayed-type hypersensitivity reactions. This effect is observed only at low doses where heparin does not exert an anticoagulant effect. The absence of these positive effects at high heparin doses with anticoagulant effect suggests that heparinase inhibition occurs independent of the anticoagulant effect and is not a competitive bioeffect. The negative effect of heparin on heparinase expression by T cells is thought to devise from a direct interaction between heparin and T lymphocytes (4,15). Through animal studies, it was interpreted that the dose at which heparin can exert an immunomodulatory effect on humans should be approximately 1-2 mg (150-300 units) per day (5).

Heparin has a heterogeneous structure consisting of many polysaccharides. Sulfated disaccharide groups in the heparin structure are presumed to exert immunomodulatory effects (6,16). LMW heparins are obtained by chemical degradation of standard heparin. Therefore, only certain LMW heparins contain active disaccharide molecules with immunological action.

Enoxaparin is a widely used LMW heparin that conveys the immunomodulatory effects of heparin (16). The recommended daily dose for anticoagulant effect is 20-80 mg. Its immunomodulatory effects arise at much lower doses.

The first study on the immunomodulatory effects of enoxaparin in humans was performed by Ingber et al. (17). The authors investigated the effects of low-dose enoxaparin on patch test results in patients with allergic contact dermatitis and found that 8 (38%) of 21 positive reactions converted to negative after a single dose of 3 mg enoxaparin.

The first preliminary study on the therapeutic use of low-dose enoxaparin in dermatology arena was published by Hodak et al. (8). In their study, 3 mg enoxaparin was administered subcutaneously once a week for 4-6 weeks to 10 patients with extensive lichen planus, and complete remission was observed in 8 of 10 patients at the end of the treatment period. Histopathological improvement was also noted in biopsy samples of 4 clinical responders. In another study, Stefanidou et al. (9) explored the therapeutic efficacy of enoxaparin in patients with lichen planus and reported complete remission in 11 of 18 patients and significant improvement in 2 patients. In their study, patients were administered 3 mg of enoxaparin weekly subcutaneously for a total of 6-13 weeks. No local or systemic side effects were observed in any of the patients. These encouraging early preliminary studies were followed by other international research in the succeeding years. In the literature, there are mostly open-ended and non-randomized studies involving a small number of patients and investigating the efficacy of subcutaneous enoxaparin in lichen planus (18-22). In the single randomized study, Iraji et al. (23) compared the efficacy of low-dose enoxaparin with oral prednisolone and concluded that, although its therapeutic efficacy is lower than that of oral prednisolone, low-dose enoxaparin has therapeutic efficacy in lichen planus and that it may be a safer treatment alternative with fewer side effects.

It is not known exactly by which mechanism(s) enoxaparin improves lichen planus. In active lichen planus lesions, there is accumulation of fibrin and fibrin degradation products in the dermoepidermal junction area, around the lymphocytic infiltration. Although fibrin deposition is not pathognomonic for lichen planus, it is a very characteristic finding. This finding might implicate that lymphokines released in lichen planus are responsible for activation of

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the coagulation system. However, the dose of enoxaparin utilized in studies is low and does not exert an anticoagulant effect. It may therefore be deduced that the efficacy mechanism of enoxaparin in lichen planus is not through its effects on the coagulation system. It is plausible that its efficacy mechanism could be through inhibition of the heparinase enzyme, involved in T lymphocyte recruitment and accumulation in target tissues. In addition, large amounts of proinflammatory cytokines such as TNF-α, granulocyte/macrophage colony simulating factor, IL-1β, IL-6, and chemokines are produced by keratinocytes in lichen planus (24). Keratinocytes, through these cytokines, chemokines, and adhesion molecules, can interact with fibroblasts, endothelial cells, and lymphocytes; the outcome is inflammation and cytotoxic destruction of keratinocytes by T lymphocytes. It is known that heparin inhibits TNF-α, which is one of the key molecules in the emergence of inflammation (9). Thus, inhibition of TNF-α might represent another alternative mechanism in enoxaparin's efficacy in lichen planus. TNF-α is also an important cytokine in the pathogenesis of psoriasis and TNF-α levels are increased in lesional and nonlesional skin and serum of patients with psoriasis (25). Considering that T lymphocytes and keratinocytes are the cells that play pivotal roles in the pathogenesis of psoriasis as well as lichen planus, it can be extrapolated that enoxaparin may also be effective in the treatment of psoriasis. However, there is no published study on the efficacy of enoxaparin in psoriasis hitherto.

In our preliminary study, we investigated the efficacy of low-dose enoxaparin in the treatment of psoriasis. For this purpose, we administered subcutaneous weekly injections of 5 mg enoxaparin to 23 patients with chronic plaque and guttate type psoriasis for 6 weeks. The injected dose was high enough to exert immunomodulatory effects, yet low enough to avoid anticoagulant effects. We evaluated the clinical efficacy of enoxaparin in psoriasis, using the PASI scoring system. There was a statistically significant difference between the PASI scores of patients at the baseline (before treatment) and PASI scores at the end of the treatment (after the 6th dose of enoxaparin) (p=0.008). At the end of the treatment, 74% of the patients had a decrease in the PASI scores: significant and moderate responses were noted in 17%, and 35% of patients, respectively. There was no significant reduction in PASI scores in 22% of treated patients. Based on these findings, there was a positive response (significant or moderate improvement) to enoxaparin in 52% of patients with psoriasis.

In our study, there was no correlation between the alteration (decrease or increase) in PASI scores and gender, age of onset of psoriasis, duration of psoriasis, clinical form of psoriasis (plaque or guttate) and previous treatments. However, the positivity rate of family history of psoriasis was 70% in our study group, which was rather higher than the normally expected 1/3 rate within the psoriasis population. It was remarkable that all 6 patients, whose PASI scores increased at the end of the treatment, had a positive family history. Three of these 6 patients had previously received both systemic therapy and phototherapy. Familial psoriasis is intractable and typically refractory to therapy. We believe that higher family history positivity rate in our study may have negatively influenced the response to enoxaparin treatment.

The dose of enoxaparin (5 mg/week) used in our study was far below the dose exerting an anticoagulant effect. We reflect that its possible mechanism of action in psoriasis is through immunomodulatory effects, as in other T cell-mediated dermatoses such as allergic contact dermatitis and lichen planus. Inhibition of heparinase enzyme or inhibition of TNF-α might account for enoxaparin's beneficial therapeutic efficacy in psoriasis.

A potential pathogenetic mechanism in T-cell-mediated disorders with epidermal proliferation and Koebner phenomenon is autocrine dysregulation. Abnormal epithelial proliferation occurs because of endogenous production of various polypeptide growth factors and activation of their corresponding receptors. It is assumed that part of immunomodulatory effects of heparin and its derivatives could arise from binding to some growth factors and inhibiting them from binding to their own receptors.

Amphiguline is a growth factor from the epidermal growth factor family, like EGF and TGF-α, and stimulates fibroblast and keratinocyte proliferation. EGF, TGF-α, amphiregulin and heparin-binding EGF-like growth factor act by binding to a common receptor in the tyrosine kinase structure, named the epidermal growth factor receptor (EGFR). While EGF and TGF-α do not require any cofactor to bind to the receptor, amphiregulin and heparin-binding EGF-like growth factor need a heparin sulfate proteolytic as an essential cofactor to bind to the receptor. It is thought that exogenous heparin-like glycosaminoglycans competitively inhibit this proteolytic cofactor and block the binding of growth factors to their receptors, thereby inhibiting autonomous keratinocyte proliferation (7,26). Thus, blockage of growth factor function might represent a third mechanism for enoxaparin's efficacy in psoriasis.

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No systemic side effects related to treatment were observed in our study group. No abnormality was detected in the laboratory tests performed during and after the treatment. As the only local side effect, ecchymosis at the injection site was observed. Although these findings suggest that low-dose enoxaparin therapy is quite safe, it should be kept in mind that rare side effects such as hypersensitivity reactions may develop independent of the dose.

In conclusion, low-dose enoxaparin represents a candidate novel therapeutic alternative in psoriasis and has a favorable side-effect profile. In terms of efficacy, further large-scale studies are warranted to determine the appropriate dosage and duration of therapy, the target psoriasis subgroup, and comparison of enoxaparin with standard psoriasis treatments.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Inequality Among Adolescents in the Developing Countries is the Main Determinant of e-Health Literacy

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ABSTRACT

Purpose: In this study, it was aimed to find out the e-health literacy levels in the adolescent age group, and its relation to adolescent decision making as well as social and economic determinants of the adolescents and their families.

Materials and Methods: The participants were 14–18 years old from 9-12 grades of the high schools at the different socioeconomic settlements in Turkey. The data was collected using a data collection form consisting of questions related to the adolescents and the socio-demographic characteristics of their parents, Adolescent Decision Making Scale and E-Health Literacy Scale for Adolescents. Data was collected from 1,082 adolescents aged 14 to 18 years.

Results: The e-health literacy level increases with the age of the adolescents, the monthly income of the family, adolescent decision making scores. Economic status and age of the adolescents are the main factors to form their e-health literacy.

Conclusion: There is an urgent need to improve e-health literacy education aiming to teach to adolescents how to find reliable health information and make appropriate decisions to prevent their own health. The e-health information literacy and services should be provided to the adolescents in low socioeconomic status as social policies of the governments in the developing countries.

Keywords: adolescents, information technology, e-health literacy, inequality, developing country

Gelişmekte Olan Ülkelerde Adölesanlar Arasındaki Eşitsizlik E-Sağlık Okuryazarlığının Temel Belirleyicisidir

ÖZET

Amaç: Bu çalışmada, adölesan yaş grubundaki e-sağlık okuryazarlık düzeylerinin, adölesan karar verme süreçleri ile adölesanların ve ebeveynlerin sosyal ve ekonomik belirleyicileri ile ilişkisinin ortaya çıkarılması amaçlanmıştır.

Methods: Katılımcılar Türkiye'deki farklı sosyoekonomik yerleşimlerdeki liselerin 9-12. sınıflarında okuyan 14-18 yaş grubudur. Veriler, adölesanların ve ebeveynlerinin sosyo-demografik özelliklerine ilişkin sorulardan oluşan veri toplama formu, Ergen Karar Verme Ölçeği ve Adölesanlar için E-Sağlık Okuryazarlığı Ölçeği kullanılarak toplanmıştır. Veriler, 14 ila 18 yaşları arasındaki 1.082 adölesandan toplanmıştır.

Results: Adölesanların yaşı, ailenin aylık geliri, karar verme puanları arttıkça e-sağlık okuryazarlığı düzeyi artmaktadır. Adolesanların ekonomik durumu ve yaşı, e-sağlık okuryazarlığını oluşturan temel faktörlerdir.

Conclusions: Adölesanlara güvenilir sağlık bilgilerini nasıl bulacaklarını ve kendi sağlıklarını korumak için uygun kararları nasıl alacaklarını öğretmeyi amaçlayan e-sağlık okuryazarlığı eğitiminin acilen iyileştirilmesine ihtiyaç vardır. Gelişmekte olan ülkelerde hükümetlerin sosyal politikaları olarak düşük sosyoekonomik statüdeki ergenlere e-sağlık bilgi okuryazarlığı ve hizmetleri sağlanmalıdır.

Anahtar kelimeler: Adölesan, Bilgi teknolojisi, E-sağlık okuryazarlığı, Eşitsizlik, Gelişmekte olan ülke

Health literacy is defined as development of the ability of the people to promote and maintain health through gaining, accessing, understanding and using the health information. Internet has entered into the daily life to reach the health information, therefore the people have changed from traditionally health resources to mobile technology, the health information in the Internet has become the first easily accessible resource in the community (1,2). As a result of this change; a great majority of the population have started to use the Internet to search for the health information (3). Electronic-health information (also called e-health) has widely used as a health literacy terminology since 2000's (4). Today, the definition of e-health literacy is accepted as "using electronic sources, understanding and evaluating it, and applying the obtained health information to address and/or solve a health problem" (5–7). E-health literacy is recognized as essential for enhancing healthcare quality and health outcomes (2). E-health literacy is also accepted as an important issue for community to gain preventive behaviors against infectious and noncommunicable diseases (8).

There is a meaningful relationship between health behaviors and health literacy in the adolescent ages (9). The main healthy behaviors are being developed in the adolescent ages (6); developing decision-making and judgement skills are also very important to gain and improve health promoting behaviors, which are influencing the lifestyle and health in the future. Media literacy was also introduced as fourth level of health literacy for the adolescents by (10). It is already known that e-health literacy can support care, improve healthcare decision-making skills, and advance health knowledge and skills (11) and encourages positive changes in the decision-making procedure and the health behaviors of the people (12), which, in turn, could empower them to better manage their health problems. It was reported that internet usage was correlated with adolescent patients and e-health literacy (3,13). Wartella et all found that 84% of 13-18 years old adolescents had obtained health information on the Internet at least once before, 38% searched online for health information once a year, and 24% searched for online health information at least monthly or more frequently in USA (14). Hove et all showed that the Internet was the most suitable environment for dissemination of health information and also the promotion of health among adolescents (15). On the other hand, adolescents with insufficient e-health literacy may be exposed to false information from low-quality health sources through the Internet (14). According to Change et all, adolescents can have difficulty in using and understanding online health information,

although they use information technologies frequently (16). It was reported that there was a need for safe browsing by adolescents, especially on important health subjects, as incorrect, misleading, and low-quality information on the Internet could result in major problems (5,6). As the world has been transforming into a more compact and well-connected locale, the information and messages on the Internet can reach and affect adolescents living across.

Media exposure has also increased very sharply among adolescents in the developed and developing countries; 98% of the adolescents use the internet every day and this rate is higher compared to the rate of all the other age groups in USA (17) and the percentage of internet use was 90.4% among 13-15 years old children in Turkey, which is a developing country. The percentage of the children who can access to Internet at their own homes was 81.2% and 71.1% of them reached through their mobile phone in Turkey (18,19). Despite the high percentage of internet access like Turkey, there is a scarcity of studies focusing on the e-health literacy levels of adolescents in the developing countries (20–22). For these reasons, we aimed to find out the e-health literacy levels in the adolescent age group, and its relation to adolescent decision making as well as social and economic determinants of the adolescents and their families.

MATERIAL AND METHODS

Ethics committee approval was received from University Noninvasive Clinical Trials Ethics Committee (Number: GO18/231-18) to assess the ethical suitability of the study. Written permission was received from the Ministry of National Education to conduct the study. In addition, the written consent of each adolescent participating in the study was obtained. The written consent of their parents and the permission of the relevant institution were also received.

Participants
This study was conducted in Ankara, the capital city of Turkey. The participants were 14–18 years old from 9-12 grades of the high schools at the different socioeconomic settlements. Adolescent age group was determined as the target population; because the capacity of decision making is developed during this age group, also they can understand and answer the questionnaire on the concept of e-health literacy.

According to the Turkish Statistical Institute (TurkSTAT) and Provincial Directorate of National Education, the

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settlements and high schools were determined as low, medium and high socioeconomic levels. One school from each socioeconomic level was selected randomly, and the total numbers of the students at the selected schools were 1782. It was aimed to reach to all the students, but 1082 students volunteered to participate in the study; the participation rate was found as 60.7%. Therefore, our study was a descriptive research for three schools from different socioeconomic settlements.

Inclusion criteria were determined as being at the school at the time of the data collection, parents' permissions and the adolescents' willingness to participate in the study.

Data Collection Tools

The questionnaire of the study composed of three main sections. The aim of the first part of the questionnaire was to determine social and economic characteristics of the adolescents and their families, also including having a cell phone/a computer, using the Internet, spending time on the Internet, and reading about health issues in general and their own health problems on the Internet (16,21,23,24). The second part of the questionnaire included the E-Health Literacy Scale for Adolescents developed by Norman and Skinner (2006). The scale has eight items that aim to assess the individual's knowledge, comfort, and perceived skills in finding, evaluating, and applying, e-health information to health problems (24). A Turkish reliability and validity study of the e-Health Literacy Scale for Adolescents was conducted by Coşkun and Bebiş in 2014 (25). The scale was reported as a reliable tool with an alpha of 0.88 in the original study, and the same Cronbach's alpha coefficient was found in the Turkish study (0.88). The responses from 'strongly agree' to 'strongly disagree' are scored on a five-point Likert scale. The minimum score of the scale could be "8" and the maximum "40". Higher scale scores indicate high levels of e-health literacy. The third part of the questionnarie included The Adolescent Decision-Making Questionnaire developed to examine the decision-making styles of adolescents (26). The questionnaire has 30 items and is responded on the basis of a four-point rating (0 = Never Applies to Me, 3 = Always Applies to Me). The questionnaire has five subscales: self-esteem in decision-making, cautious selectivity, negligence, panic and evading responsibility. Each subscale has six items and the scores to be obtained for the subscales range from 0 to 18. Highness of self-esteem in decision-making scores indicates highness of self-respect level. Highness of scores of the other subscales indicates that the relevant decision-making style is used more frequently. The questionnaire was adapted into Turkish by Çolakkadıoğlu and Güçray (27). In the confirmatory and exploratory factor analyses which were performed to test the construct validity of the questionnaire, it was seen that 30 items in the Turkish form of the questionnaire were loaded over five factors, as in the original form. The Cronbach's alpha internal consistency reliability coefficient obtained for measurements acquired from the questionnaire was found to be between 0.65-0.79 and the test-retest consistency was found to be between 0.80-0.86 for the subscales. Cronbach'salpha for the present sample was calculated as 0.73.

Data Collection

The schools were visited and informed about the research, and the data collection date was determined with the principal of the high school. The parents' consents forms were sent to the families by the principal of the high schools three days before data collection. All the adolescents were answered the questionnaires at the same lecture hour to avoid the information contamination among the students.

The data was analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, 23.0, a packaged software. The descriptive characteristics of the adolescents and their parents were presented by the numbers, percentages, mean, and standard deviation values. T-test was used in the comparison of the quantitative and continuous data between any two independent groups; on the other hand, a one-way ANOVA test was used in the comparison of the quantitative, continuous data among more than two independent groups.

The level of significance was taken to be $p < 0.05$. The predictors of e-health literacy in adolescents were analyzed using linear regression models. E-health literacy was accepted as dependent variable, the independent variables found statistically significant in the descriptive analyses were included in the regression model. The variables in linear regression model were individual factors (age, gender, decision making scale), family factors (father's educational level, numbers of siblings, health care worker in the family), economic factors (monthly family income, having a computer) and the behavior of searching health-related information on the internet (about own health and health subjects). Also, Tukey's HSD post-hoc analysis was performed to determine between which groups, the significant differences obtained as a result of ANOVA exactly occurred.

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RESULTS

Data was collected from 1,082 adolescents aged 14 to 18 years; 56% of the adolescents were male. The mean age of the participants was 15.9 (±1.1) years old, and 79.3% of the participants were between the ages of 15 and 17 years.

In the study, the mean score of e-health literacy for adolescents was found as 26.9 (± 7.6) with the range of 8 to 40. Female adolescents had significantly higher e-health literacy levels than males (p<0.001). The level of e-health literacy increases, as the age of the adolescents increases (p <0.001); the numbers of siblings decreases (p=0.007); the adolescents with chronic disease (p=0.045); the education level of the father increases (p=0.001); the monthly family income increases, and having a healthcare worker in the family (p<0.05) (Table 1). The mean score of adolescent decision-making scale was found as 39.5 (± 10.0) with the range of 9-85. The adolescents from the school in high economic settlement had the higher e-health literacy level (28.6±6.9) than the adolescents from the school in the low economic settlement (26.3±7.6) and adolescents from the school in the middle economic settlement (25.7±7.9) (p<0.001). (table is not given)

E-health literacy levels of the adolescents increases with accessing the Internet through cell phones (p<0.05), having a computer (p<0.05), the duration of internet usage on weekdays increases (p<0.05) and on the weekends (p<0.001), and reading the general health information (p<0.001) and their own health problems (p<0.001) on the internet (Table 2).

In the linear regression model, the e-health literacy level increases with the age of the adolescents (p<0.05), the monthly income of the family (p<0.05), adolescent decision making scores (p<0.001); but an increase in the number of siblings (p<0.05) caused a decrease in e-health literacy scores (Table 3).

DISCUSSION

The aim of this study was to find out the e-health literacy levels in the adolescent age group, and its relation to adolescent decision making as well as social and economic determinants of the adolescents and their families. It was found that individual development stage of the adolescent such as age and decision making capacity, also economic statuses of the parents had a positive relation with the e-health literacy levels of the adolescents.

In the study, it was found the "e-health literacy" total mean score of the adolescents was 26.9 ±7.6, and they used the Internet at a high rate. Similar results have been obtained in some other studies across the world; the e-health literacy mean scores have been found to be 26.0 in a study conducted in Serbia by Gazibara, et al. with adolescents in the age group of 14–19 years (28), 30.6 in a study conducted in USA by Ghaddar, et al. with adolescents in the age group of 14–20 years (29), and 22.6 in a study conducted in Taiwan by Chang, et al. (2015) with high school students (from 7th, 8th, and 9th grades) (16). The e-health literacy levels among adolescents were quite similar in different countries with different opportunities and cultures. E-health literacy has become widespread all over the world due to electronic communication emerging within the scope of globalization.

According to bivariate analyses of our data, gender, health care workers in the family, having chronical disease, duration of internet usage were the significant determinants for the level of e-health literacy.

Females showed higher e-health literacy levels compared to the males. Gazibara, et al. (2019) determined that females had higher e-health literacy in USA. This was stated to be related to the fact that female adolescents generally used the websites on health more frequently compared to male adolescents (28). Also, many other studies support the opinion that female adolescents are more interested in health subjects, and they have more positive health behaviors compared to male adolescents (11,23).

Chang et al. observed that the adolescents whose parents had low levels of education had lower e-health literacy levels (16); we also had the same finding. The e-health literacy levels of the adolescents increased as the higher education levels of the fathers in our study. However, it did not have a significant impact based on the education statuses of the mothers. This situation could be caused by the fact that in Turkey, men could reach high school and university education more than the women could; therefore the educational levels and health literacy levels of women remained lower than those of the men (23,30).

In this study, healthcare worker in the family played an important role in increasing the level of e-health literacy among adolescents. Many studies have determined that the health care professionals are one of the important health information sources to access health information for the adolescents (29,31).

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Table 1. Mean e-health literacy scores of the adolescents by social and economic characteristics of the adolescents and their families (n=1082)				
	n	%	Mean e- HL± SD[a]	p
Gender				
Female	476	44.0	27.5±6.3	0.000
Male	606	56.0	26.4±8.4	
Age				
14	142	13.1	24.6±7.6	0.000
15	288	26.6	26.6±7.5	
16	239	22.1	26.9±7.9	
17	331	30.6	27.5±7.3	
18	82	7.6	28.7±7.4	
Chronic disease				
Having chronic illness	100	9.2	29.1±6.8	0.045
Not having chronic disease	180	16.7	26.9±8.1	
Not having any disease	802	74.1	26.5±7.5	
Family type				
Extended	107	9.9	26.3±7.9	0.164
Nuclear	837	77.4	26.9±7.6	
With single parents and relatives	138	12.8	27.0±7.1	
Number of sibling				
0	83	7.7	28.4±7.3	0.007
1	471	43.5	27.5±7.3	
2 and more	528	48.8	24.5±7.6	
Mother's educational level				
Illiterate	34	3.1	25.4±8.7	0.654
Literate	19	1.8	24.7±6.7	
Primary school	266	24.6	27.3±7.4	
High school	289	26.7	26.4±7.5	
University	352	32.5	27.1±7.8	
Post graduate education	122	11.3	27.3±7.1	
Mother's employment status				
Employed	361	33.4	27.2±7.5	0.855
Unemployed	720	66.6	26.7±7.5	
Father's educational level				
Illiterate	16	1.5	24.7±8.4	0.001
Literate	4	0.4	19.3±6.9	
Primary school	170	15.7	26.1±7.6	
High school	245	22.6	26.3±6.9	
University	431	39.8	27.5±7.8	
Post graduate education	216	20.0	27.2±7.6	
Father's employment status				
Employed	968	89.5	26.9±7.6	0.449
Unemployed	113	10.5	26.4±6.9	
Monthly family income				
1000 TL and lower	19	1.8	25.1±6.5	0.000
1001-2000 TL	243	22.5	25.5±7.4	
2001-3000 TL	336	31.1	26.4±7.7	
3001-5000 TL	282	26.1	27.7±6.9	
5001 TL and over	202	19.7	28.4±8.2	
Having a healthcare worker in the family				
Yes	103	9.5	28.5±6.4	0.022
No	979	90.5	26.7±7.7	

Note. SD= standard deviation; TL= Turkish lira.

Table 2. Mean e-health literacy scores of the adolescents by having internet accessibility (n=1082)				
Internet accessability	n	%	Mean e-HL ± SD[a]	p
Having a cell phone				
Yes	1039	96.0	26.9±7.6	0.056
No	43	4.0	24.7±7.1	
Internet access though cell phone				
Yes	1000	92.4	27.0±7.5	0.016
No	82	7.6	24.9±8.2	
Having a computer				
Yes	767	70.9	27.4±7.6	0.002
No	315	29.1	25.7±7.5	
Duration of internet usage on weekdays				
60 minutes and less	160	14.8	25.3±8.3	0.001
61-119 minutes	220	20.3	26.6±7.2	
121-179 minutes	284	26.2	27.4±6.6	
180 minutes and more	418	38.6	27.3±8.1	
Duration of internet usage on weekends				
60 minutes and less	118	10.9	23.4±9.2	0.000
61-119 minutes	154	14.2	27.0±6.3	
121-179 minutes	200	18.5	27.4±7.1	
180-239 minutes	237	21.9	27.5±6.7	
240 minutes and more	373	34.5	27.3±8.0	
Reading the general health information on the internet				
Yes	652	60.3	27.9±7.2	0.000
No	430	39.7	25.3±7.9	
Reading the health information for their own health problems on the internet				
Yes	396	36.6	28.3±7.2	0.000
No	686	63.4	26.1±7.7	

[a]*SD= standard deviation*

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Table 3. Multiple linear regression predicting adolescents' e-health literacy (n =1082)							
						95% CIs for B	
Variable	B	SE	Beta	T	P	Lower	Upper
(Constant)	19.940	4.134		4.824	0.000	11.829	28.051
Gender	0.494	0.461	0.032	1.072	0.284	-0.410	1.399
Age	0.578	0.191	0.090	3.023	**0.003**	**0.203**	**0.954**
Number of siblings	-0.577	0.194	0.089	-2.975	**0.003**	**-0.958**	**-0.196**
Monthly family income	0.468	0.206	0.071	2.277	**0.023**	**0.065**	**0.871**
Father's educational level	0.494	0.461	0.032	1.072	0.284	-0.410	0.494
Having a healthcare worker in the family	0.933	0.762	0.036	1.224	0.221	2.428	0.562
Having a computer	0.935	0.504	0.056	1.856	0.064	1.923	0.053
Reading the general health information on the internet	1.791	0.483	0.115	3.704	<0.001	2.740	0.842
Reading the health information for their own health problems on the internet	1.201	0.491	0.076	2.448	0.015	2.164	0.238
Having chronic disease	0.336	0.355	0.031	1.032	0.302	1.062	0.390
Adolescent decision making questionnaire	0.094	0.022	0.124	4.196	**0.000**	**0.050**	**0.138**

The communication technologies to access health information have developed dramatically in the last ten years and continue to develop rapidly (20). Adolescents also evaluate the content of the information they obtain via the Internet and use the information to solve their health problems in their daily lives (32). In this study, most of the adolescents in the age group of 14–18 years (60.3%) stated that they used the Internet to obtain information about their health. In a study by Chang (2015), it was determined that the rate of searching for online health information among internet-using adolescents was 61% (16). Also, in this study, the e-health literacy levels of adolescents with a chronic disease were found to be higher. Chisolm et al. (2011) determined that 50% of adolescents with asthma and diabetes used the Internet to obtain health information (33). The people with high e-health literacy skills are aware that they should go into action when having a serious health issue. Therefore, adolescents with chronic diseases performed more searches for health information (34). In a study by Park, it was determined that adolescents with asthma, disk hernia, and atopic dermatitis had lower e-health literacy levels compared to healthy adolescents (22). Although health literacy – relevant skills are mainly developed on the needs of the adolescent (35), it is very important for the adolescents how to be aware of their needs to be healthier.

Besides the significant variables found in the bivariate analyses, mainly adolescent development stage and economic determinants found the most significant determinants in our further analyses. In the present study, it was determined that as the age of the adolescents increased, the e-health literacy level increased. This result can be explained by the fact that the age of the adolescents and their awareness levels increased with their cognitive and social development. As the age and the grade of the adolescents increase, e-health literacy increases their ability to search for health information on the Internet (24). It is already known that decision making and judgement skills are improved with the development of the frontal lobe of the brain in the adolescence period of the life (9). Adolescents stated that they used health information found on the Internet for their health-related decision making, if they found it reliable after evaluation (16). Health-literacy is considered as a combination of the personal characteristics and cognitive skills in the adolescence (35). With increasing age, brain development also affects the increase in health literacy. In our study, both age and decision-making scale were found the important determinants to increase of the e-health literacy levels of the adolescents. Therefore, further studies can help to find the most effective and age-specific strategies to improve e-health literacy among the adolescents, as promoting e-health literacy among adolescents is an important strategy to pave way for positive health behaviors in life (29). This age-specific strategies and intervention studies should be developed consider of the development stage of the brain in the adolescent ages.

In improving the health-literacy skills in the adolescents, it is important to establish the convenient environmental

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settings, which are increasing the adolescents' motivation on searching and learning health information through internet. It has been observed in the literature that those in late adolescence had higher health literacy compared to those in early adolescence; it has also been determined that the accessibility to facilities to search for health information via the Internet was lower in the early adolescence period (20,29,33). In a study conducted in Spain, it was reported that the education provided in secondary schools developed e-health literacy among adolescents (36). In this study, as family income levels and having a computer, the e-health literacy levels also increased in the adolescents. Having fewer siblings can be also accepted as indicators of nuclear family, and an economic status in Turkey. It is shown that the children from lower socioeconomic backgrounds had lower e-health literacy levels than the children from higher socioeconomic levels; our finding is similar to the previous studies demonstrated that adolescents in lower socioeconomic levels, used the Internet less, exhibited lower online health information search behaviors and lower e-health literacy levels than the adolescents in the higher socioeconomic levels (37–39).

Accessing health information on the Internet by adolescents was considered a social privilege. The results of this study also indicate that there is a need to improve e-health literacy levels among adolescents, especially for those from low socioeconomic backgrounds. Having access to accurate and reliable health information is also a human right as it is declared as "*Basic health services and access to information are the priority issues*" in Astana Declaration (40). In this context, the Internet and electronic environment provide a new opportunity for adolescents to acquire health education, and becoming more necessary in our life. However, it is also required that adolescents should be protected from misinformation and disinformation on the Internet. We have already learned how infodemic affect the people's knowledge and behaviors of the people in COVID-19 pandemia (41). There is an urgent need to improve e-health literacy education aiming to teach to the adolescents how to find reliable health information, evaluate the content, and make appropriate decisions to promote and prevent their own health. E-health literacy programs for adolescents should be integrated into the school health education syllabus to strengthen the adolescents' life skills (42).

During COVID-19 pandemia, we have also observed that social inequality among adolescents in developing countries, are the main barriers in front of the technologies (43). United Nations Committee on the Rights of the Child recommended that states parties should encourage the use of digital technologies to promote healthy life styles, also

research and development focused on children's health needs (44).

In our study also showed that the adolescents from lower socioeconomic level had lower e-health literacy levels. Inequal access of communication technology will increase the inequality between social classes and strata, the adolescents in lower socioeconomic level of the developing countries will be the most vulnerable adults to reach the accurate health information on the internet in the world. For this reason, the e-health information literacy and services should be provided to the adolescents in low socioeconomic status as social policies of the governments in the developing countries. New communication technology and e-health literacy education will be introduced to the adolescents living in disadvantage communities.

Limitations
There are some limitations to this study, as well. The sample of this study was selected from high schools with three different socioeconomic levels from the capital city of the country. However, it is assumed that high school students living in little towns and rural areas might have lower accessibility of Internet than urban settlements. Another limitation is that the internet usage behavior of the high school students and the e-health literacy of their parents, which may influence the e-health literacy levels and health outcomes, have not been assessed in this study. Further studies are required to examine the longitudinal effects on the e-health literacy of adolescents.

Conclusions and Future Directions
This study is the first research in Turkey, describing the e-health literacy levels of high school students and related to the variables of economic statuses and mental development. In the study, the inequality such as economic statuses come into prominence, affecting e-health literacy. The results of this study are important for decision makers, school health professionals, public and pediatric health care providers.

The results of this study add to the literature concerning the variables related to the e-health literacy levels and the health of adolescents in developing countries. Understanding the variables of health characteristics or statuses and the socio-demographic factors helps to design the content of training on e-health literacy interventions and achieve effective e-health literacy levels. This study has revealed that e-health literacy should be developed among adolescents; for this, training programs suitable for the developmental period should be organized in the schools.

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Etiological Evaluation of Patients with Hepatomegaly, Splenomegaly, and Hepatosplenomegaly Referred to a Pediatric Metabolism Unit

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ABSTRACT

Objective: Hepatomegaly, splenomegaly, and hepatosplenomegaly in children can be due to various disorders, and also inborn errors of metabolism (IEM). Some IEM's have specific treatments which should be started before irreversible complications occur. The aim of this study is to evaluate the etiological causes of visceromegaly in pediatric patients, and assess the clinical findings of patients having an IEM.

Materials, and Methods: In this study, medical records of 93 patients who were referred to a Pediatric Metabolism Unit in a tertiary care hospital with the suspicion of IEM-related hepatomegaly, splenomegaly, or hepatosplenomegaly were reviewed retrospectively.

Results: 45 patients had hepatomegaly, 18 had splenomegaly, and 30 had hepatosplenomegaly. A total of 52 patients were diagnosed as having an IEM. In hepatomegaly group; diagnoses were glycogen storage disease (GSD)(51,1%), cholesteryl-ester storage disease (4,4%), galactosialidosis (4,4%), mucopolysaccharidosis (4,4%), multiple-acyl-CoA dehydrogenase deficiency (2,2%), hereditary fructose intolerance (2,2%), and GM1 gangliosidosis (2,2%). In splenomegaly group; diagnoses were Gaucher disease (22,2%), Niemann-Pick disease type C (NPC)(16,6%), and Niemann-Pick disease type A/B (NPAB)(11,1%). In hepatosplenomegaly group; diagnoses were Gaucher disease (13,3%), NPC (6,6%), NPAB (6,6%), GSD (3,3%), mucopolysaccharidosis (3,3%), and infantile sialic acid storage disease (3,3%). 32 patients were lost to follow-up. The eventual diagnoses of 9 patients were not IEM.

Conclusion: IEMs present from the prenatal period to adulthood. Awareness of clinicians, and diagnostic algorithms can prevent delayed diagnosis, and enable early treatment for treatable IEMs or provide genetic counseling for the patient's family.

Keywords: hepatomegaly, splenomegaly, hepatosplenomegaly, inborn errors of metabolism

Çocuk Metabolizma Ünitesine Hepatomegali, Splenomegali ve Hepatosplenomegali Nedeniyle Sevk Edilen Pediatrik Hastaların Etiyolojik Değerlendirmesi

ÖZET

Amaç: Çocuklarda hepatomegali, splenomegali ve hepatosplenomegali; pek çok hastalığa ve ayrıca kalıtsal metabolik hastalıklara (KMH) bağlı olarak görülebilir. Bazı KMH'ların spesifik tedavileri olup geri dönüşsüz komplikasyonlar gelişmeden başlanması gereklidir. Bu çalışmanın amacı pediatrik hastalarda viseromegali etiyolojisinin değerlendirilmesi ve KMH tanısı alan hastaların klinik bulgularının irdelenmesidir.

Gereç ve Yöntem: Bu çalışmada, üçüncü basamak bir hastanede KMH'a bağlı hepatomegali, splenomegali ve hepatosplenomegali olduğundan şüphelenilerek Çocuk Metabolizma Bölümü'ne sevk edilen 93 hastanın tıbbi kayıtları geriye dönük olarak incelenmiştir.

Bulgular: 45 hastada hepatomegali, 18 hastada splenomegali ve 30 hastada hepatosplenomegali saptandı. Toplam 52 hasta KMH tanısı aldı. Hepatomegali grubunda tanılar glikojen depo hastalığı (GSD)(51,1%), kolesteril ester depo hastalığı (4,4%), galaktosiyalidozis (4,4%), mukopolisakkaridozis (4,4%), multipl-açil-KoA dehidrogenaz eksikliği (2,2%), herediter fruktoz intoleransı (2,2%) ve GM1 gangliyosidozis (2,2%) idi. Splenomegali grubunda tanılar Gaucher hastalığı (22,2%), Niemann-Pick hastalığı tip C (NPC)(16,6%) ve Niemann-Pick hastalığı tip A/B (NPAB)(11,1%) idi. Hepatosplenomegali grubunda tanılar Gaucher hastalığı (13,3%), NPC (6,6%), NPAB (6,6%), GSD (3,3%), mukopolisakkaridozis (3,3%), and infantil siyalik asit depo hastalığı (3,3%) idi. 32 hasta klinikte takibe devam etmedi. 9 hastaya KMH dışında tanılar konuldu.

Sonuç: KMH'lar prenatal dönemden erişkin yaşlara kadar bulgu verebilmektedir. Klinisyenlerin farkındalığının arttırılması ve tanısal algoritmalar, tanıda gecikmeyi engelleyebilir ve tedavisi olan KMH'lar için erken tedaviyi ve hastaların ailelerine genetik danışma verilebilmesini sağlayabilir.

Anahtar Kelimeler: Hepatomegali, splenomegali, hepatosplenomegali, kalıtsal metabolik hastalıklar

The etiology of hepatomegaly (HM), splenomegaly (SM), or hepatosplenomegaly (HSM) in a pediatric patient is associated with infections, genetic liver diseases, hematological diseases, or malignancies, auto-immune disorders, passive congestion as well as inborn errors of metabolism (IEM) (1,2). Visceromegaly is an important finding in pediatric patients referred to investigate underlying etiology. Extensive diagnostic is usually needed in such patients. A national etiological study regarding splenomegaly was reported which was conducted in both pediatric, and adult patients, and none of the patients were diagnosed as having an IEM. The most frequent diagnoses were hematological conditions in this study (1). Clinicians usually investigate frequent non-IEM disorders in the beginning, and when the etiological workup does not bring diagnosis when an IEM is suspected. Timely diagnosis of an IEM enables genetic counseling providing future healthy pregnancies for the patient's family and specific therapeutic interventions before the development of irreversible complications for treatable IEM's. The purpose of this study is to uncover the etiological causes of visceromegaly in pediatric patients who were suspected to have an IEM.

MATERIALS and METHODS

Sample

Medical records of pediatric patients who were admitted to Adana City Research, and Training Hospital, Pediatric Metabolism Department between December 2018, and December 2020, and had hepatomegaly, splenomegaly, or hepatosplenomegaly were reviewed retrospectively. Accordingly, the sample of the study included 93 patients. Hepatomegaly, splenomegaly, or hepatosplenomegaly were defined as enlargement of the liver, and/or spleen according to patient's age either detected by physical examination of two separate clinicians or by ultrasonography (3). Sociodemographic data (gender, age, nationality, parental consanguinity, similar family history, clinicians that referred the patients, current status of patients), growth parameters (weight, and height), clinical, laboratory, and imaging findings, and eventual diagnoses of patients were noted. Eventual diagnoses of patients were confirmed by enzyme analyses, and/or molecular analyses.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 23.0, Chicago, IC, USA) program was used for statistical analysis. Results were presented as mean, and standard deviation for numerical variables, and frequency, and percentage for categorical data. The normality of the quantitative data was evaluated by using the Kolmogorov-Smirnov test. To assess non-parametric data the Mann Whitney U test was used to compare numerical variables between two independent groups, and the Kruskal-Wallis test was used in comparing more than two independent groups. p values <0.05 were accepted as statistically significant.

RESULTS

There were 93 patients with visceromegaly; of which 45 had hepatomegaly, 18 had splenomegaly, and 30 had hepatosplenomegaly. 36 were female, 57 were male. 43% of the patients were Syrian refugees. 78,5% of patients had parental consanguinity, and 34,4% had a positive family history. Patients' mean current age was 56,9±49,8 months. 10 patients died during follow-up. 32 patients were lost to follow-up during the COVID-19 pandemic. Patients were referred due to suspicion of an IEM by pediatricians (47,3%), pediatric gastroenterologists (33,3%), pediatric hematologists (16,1%), pediatric neurologists (2,2%) or pediatric endocrinologists (1,1%). None of the patients had lymphadenopathy. None of the patients had splenectomy.

Patients were reviewed according to groups. In the hepatomegaly group; eventual diagnoses were glycogen storage disease (GSD) in 23 patients (51,1%), cholesteryl-ester storage disease (CESD) in 2 patients (4,4%), galacto-sialidosis in 2 patients (4,4%), mucopolysaccharidosis in 2 patients (4,4%), multiple-acyl-CoA dehydrogenase deficiency (MADD) in one patient (2,2%), hereditary fructose intolerance in one patient (2,2%), and GM1 gangliosidosis in one patient (2,2%) (Figure 1). One patient with hepatomegaly was eventually diagnosed as having alpha-1 antitrypsin deficiency. 12 (26,6%) patients without a specific diagnosis were lost to follow-up. Patients in the hepatomegaly group had the highest rate of parental consanguinity, and positive family history (Table 1). 8,9% of patients had leukopenia and were diagnosed with GSD type 1a. 8,9% had anemia, and 6,7% had thrombocytopenia (Table 2).

Specific diagnoses of the patients with isolated splenomegaly were Gaucher disease in 4 patients (22,2%), Niemann-Pick disease type C (NPC) in 3 patients (16,6%), and Niemann-Pick disease type A/B (NPAB) in 2 patients (11,1%) (Figure 1). One patient with splenomegaly was eventually diagnosed with immune deficiency. 8 (44,4%) patients had no specific diagnoses and were lost to follow-up. In the splenomegaly group; 55,6% had thrombocytopenia, 55,6% had anemia, and 16,7% had leukopenia (Table 2).

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Table 1. Sociodemographic data, growth parameters, and multisystemic involvement of patients according to type of visceromegaly											
	Total N (%)	IEM N (%)	Parental consanguinity %*	(+) family history %*	Weight SDS	Height SDS	Liver steatosis %*	Neonatal cholestasis %*	Neurological deficit %*	Eye involv. %*	Cardiac involv. %*
HM	45 (48,3)	32 (71,1)	84,4	44,4	-1,08±1,59	-1,88±1,48	53,3	6,7	11,1	2,2	4,4
SM	18 (19,3)	9 (50)	66,7	27,8	-0,77±1,45	-0,89±1,09	0	16,7	27,8	0	5,6
HSM	30 (32,2)	11 (36,6)	76,7	23,3	-1,42±1,94	-1,91±1,88	6,7	16,7	33,3	3,3	7

HM: Hepatomegaly, HSM: Hepatosplenomegaly, IEM: Inborn errors of metabolism, Involv.: involvement, N: Number, SDS: Standard deviation score, SM: Splenomegaly, (+): Positive
*: Percentage within the subgroup

Table 2. Laboratory evaluation of patients according to type of visceromegaly										
	Leukopenia %*	Anemia %*	Thrombocytopenia %*	Elevated liver enzyme %*	Low HDL levels %*	Hyperlipidemia ⧫ %*	Low blood glucose %*	Hyperuricemia %*	Elevated INR %*	Elevated AFP %*
Hepatomegaly	8,9	8,9	6,7	68,9	0	46,7	26,7	13,3	11,1	13,3
Splenomegaly	16,7	55,6	55,6	44,4	38,9	0	0	5,6	5,6	11,1
Hepatosplenomegaly	30	63,3	70	63,3	16,7	16,7	0	0	20	26,7

AFP: Alpha-fetoprotein, INR: International normalized ratio
*: Percentage within the subgroup
⧫: Hypercholesterolemia, and/or hypertriglyceridemia

Eventual diagnoses of the patients with hepatosplenomegaly were Gaucher disease in 4 patients (13,3%), NPC in 2 patients (6,6%), NPAB in 2 patients (6,6%), GSD in one patient (3,3%), mucopolysaccharidosis (MPS) in 1 patient (3,3%), and infantile sialic acid storage disease (ISSD) in one patient (3,3%) (Figure 1). Three patients with hepatosplenomegaly were diagnosed as having familial hemophagocytic lymphohistiocytosis (HLH). Two patients with hepatosplenomegaly were diagnosed with immune deficiency, one patient with tuberous sclerosis, and one patient with autoimmune hepatitis. 12 (40%) patients had no specific diagnoses and were lost to follow-up. In the hepatosplenomegaly group; 70% had thrombocytopenia, 63,3% had anemia, and 30% had leukopenia (Table 2).

Facial dysmorphism was seen in 15 patients; of which 3 patients had MPS, 2 patients had galactosialidosis, 1 patient had GM1 gangliosidosis, 1 patient had ISSD, and 8 patients did not have any specific diagnosis. Both weight SDS, and height SDS were lowest in the hepatosplenomegaly group but there was no statistically meaningful difference between the groups (p>0,05) (Table 1).

4 patients with non-immune hydrops fetalis were diagnosed as having Gaucher disease, NPC, galactosialidosis, ISSD, and two patients were undiagnosed. 3 patients with transient neonatal cholestasis were diagnosed with NPC. One NPC patient died with cholestasis and fulminant hepatic failure. The other 4 patients with neonatal cholestasis were diagnosed with MADD, ISSD, NPAB, and alpha-1 antitrypsin deficiency.

Since IEMs present with multisystemic involvement, neurological, ophthalmologic, and cardiac evaluations were also made. Neurological manifestations were observed in 2 patients with NPC, 2 patients with Gaucher disease, 2 patients with galactosialidosis, 2 patients with MPS, 1 patient with GM1 gangliosidosis, 1 patient with ISSD, 1 patient with NPAB, 1 patient with MADD, and 7 undiagnosed patients. One of the HM patients with MPS had mitral valve insufficiency, and another HM patient with galactosialidosis had mitral, and aortic valve insufficiencies. One patient with SM had mitral valve insufficiency whose diagnosis was Niemann-Pick disease type A/B. 5 patients with HSM had mitral valve insufficiency who were diagnosed as having sphingolipidosis. Cardiac rhabdomyoma was detected in a patient with tuberous sclerosis and HSM. Cherry-red spot was detected only in one patient with NPAB (Table 1). 4 patients with GSD also had renomegaly along with hepatomegaly.

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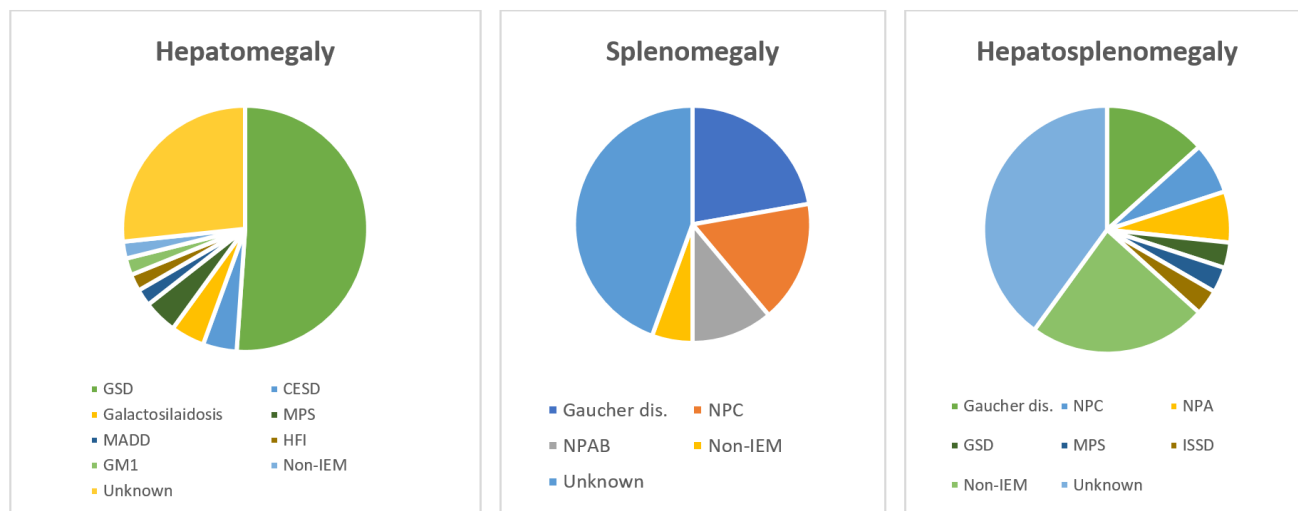
Figure 1. Specific diagnosis of patients according to type of visceromegaly
CESD: Cholesteryl-ester storage disease, dis.: Disease, GM1: GM1 gangliosidosis, GSD: Glycogen storage disease, HFI: Hereditary fructose intolerance, ISSD: Infantile Sialic Acid Storage Disease, MADD: Multiple Acyl-CoA dehydrogenase deficiency, MPS: Mucopolysaccharidosis, Non-IEM: Non-Inborn Errors of Metabolism, NPAB: Niemann-Pick disease type A/B, NPC: Niemann-Pick disease type C

On laboratory evaluation, 12 patients had hypoglycemia, and all were diagnosed with GSD. 58 patients had elevated liver enzymes, 43 of them had IEM. 12 patients had coagulopathy, 7 of them had IEM. 26 patients had hypercholesterolemia, and/or hypertriglyceridemia; 17 of them had GSD, 2 had CESD, 1 had MADD, one had immune deficiency, and 5 were undiagnosed. 12 patients had low HDL cholesterol levels; of which 6 had Gaucher disease, 2 had NPAB, 1 had NPC, 1 had familial HLH, and 2 were undiagnosed. 7 patients had hyperuricemia; diagnosis of 6 was GSD, and one was NPC. Elevated alpha-fetoprotein levels were detected in 16 patients, 3 had NPC, 2 had GDH, 1 had Gaucher disease, 1 had immune deficiency, 1 had alpha-1 antitrypsin deficiency, and 7 were without any specific diagnosis (Table 2). 18 patients had elevated acid phosphatase levels, 4 of them were without any diagnosis but 8 had Gaucher disease, 3 had NPC, 2 had galactosialidosis, and 1 had NPAB. 7 patients had elevated levels of biotinidase enzyme, 6 of them had GSD, and 1 was undiagnosed.

DISCUSSION

Hepatomegaly, splenomegaly, and hepatosplenomegaly are owing to either inherited or acquired etiologies in the pediatric population (1,2). Extensive diagnostic work-up for the specific diagnosis is needed in most cases. In the case that massive visceromegaly is present or the patient's general condition is not well, all the possible causes can be investigated simultaneously. For a patient with the possibility of having IEM, the exact diagnosis is crucial for providing the family genetic counseling. Diagnostic clues are needed to achieve this. In this study, patients in whom IEM diagnosis is anticipated, and referred to Pediatric Metabolism Department for evaluation were included. Unfortunately, regular patient follow-up was interrupted due to the COVID-19 pandemic, and a total of 32 patients were without a diagnosis and lost to follow-up. Another remarkable feature of our study population is that 43% of the patients were Syrian refugees. Considering high parental consanguinity rates, large family size, low socioeconomic status; IEMs tend to be more frequent in refugee children. Unfortunately, non-compliance to follow-up is more frequent in this group of patients.

Overall, a small number of patients (9,6%) had diagnoses other than an IEM. Probably, the reason is that these patients were referred to a pediatric metabolism specialist after certain etiological investigations, and only patients without a diagnosis were referred. Patients in this study had high rates of parental consanguinity (78,5%), and positive family history (34,4%), this is due to the high expectation of an underlying IEM in this group of patients. The most referrals in our study were from pediatricians. This may reflect an awareness of pediatricians for underlying IEM possibility of patients with visceromegaly. Patients without cytopenia were mostly referred from pediatric gastroenterologists, and patients with cytopenia were referred from pediatric hematologists. 2 patients' visceromegaly were noticed during neurological evaluation, and one patient with hepatomegaly and severe short

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height was referred from the pediatric endocrinology department.

Half of the patients with hepatomegaly had been diagnosed with GSD. Accompanying findings such as short stature, hepatosteatosis, elevated liver enzymes, hyperlipidemia, low blood glucose, and hyperuricemia are important parameters to determine the underlying pathology. In a study evaluating 38 patients with GSD, all of the patients had hepatomegaly. Similarly, elevated liver function tests, hypoglycemia, hyperlipidemia, hyperuricemia were frequently observed (4). Other less often diagnoses were lipid storage diseases, fructose metabolism defects, and fatty acid oxidation defects (FAOD).

All the patients with splenomegaly were diagnosed with sphingolipidosis; namely Gaucher disease, NPAB, and NPC. Half of these patients had thrombocytopenia, and anemia probably due to hypersplenism. One-third of the patients had low HDL cholesterol levels. One patient had cherry-red spot. Cherry-red spot is a diagnostic but not a necessary finding in the matter of diagnosing sphingolipidosis. Except for one patient with GSD, all the patients with HSM had various lysosomal storage diseases. Non-IEM patients were most frequent in this group. Two-third of the patients had thrombocytopenia and anemia, and one-third of the patients had leukopenia. Short stature, neurological findings, elevated liver enzymes, coagulopathy, and elevated AFP levels were more prominent in this group. In the study from Denmark including primary evaluation of patients only with splenomegaly from all age groups, hematological diseases (39%) were the most common etiology followed by hepatic diseases (18%), and infections (10%). None of the patients had an IEM but the authors stated that in the prospective part of the study not all of the patients were evaluated regarding Gaucher disease1. Gaucher disease is an exemplary disease; early diagnosis, and timely treatment prevents irreversible clinical manifestations. First step in the diagnostic journey is adding the disease in the differential diagnosis. Radiological evaluations frequently aid the diagnosis. Radiographs may show Erlenmeyer flask deformity of the femur pointing to Gaucher disease or dysostosis multiplex in favor of lysosomal storage diseases (2,5). Liver steatosis can be observed in GSD, fructose, and galactose metabolism disorders, CESD, and other lipid storage diseases, FAOD or mitochondrial disorders, and splenic nodules or masses can be detected in Gaucher disease (2,6). Renomegaly is another finding of GSD (4). Four of our GSD patients also had renal enlargement.

CONCLUSION

Generally, clinical findings of inborn errors of metabolism are similar to other etiologies. Accordingly; diagnosis of IEMs is delayed, these patients are subject of exhaustive, and invasive diagnostic procedures such as bone marrow aspiration/biopsy, liver biopsy, and inappropriate or unnecessary treatments. Whereas, it is possible to simply diagnose these patients with enzyme analysis or genetic tests. IEMs do not only appear in the neonatal period or infancy but present from the prenatal period to adulthood. Thus, in the case of multisystemic involvement especially neurological involvement, and subacute or chronic clinical course clinicians should include IEMs in the differential diagnosis of visceromegaly. Awareness of clinicians should be raised, and diagnostic algorithms should be established to avoid misdiagnosis or unrecognition in this group of patients.

DECLARATIONS

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Conflicts of Interest/Competing Interests
Not applicable.

Ethics Approval
Ethical approval was obtained from Adana City Training, and Research Hospital Local Ethics Committee on 27.01.2021 with the document numbered 1266/75 for the study.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Evaluation of Quality of Life Scales According to Disease Activity in Rheumatoid Arthritis

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ABSTRACT

Objective: In addition to disease activity, quality of life (QoL) of patients with rheumatoid arthritis (RA) is also related to variables like pain, fatigue, depression, anxiety, and sleep quality. We aimed to evaluate the association among disease activity and QoL scales in RA.

Methods: In this cross-sectional study, 92 consecutive RA patients who applied to Ankara City Hospital Rheumatology outpatient clinic in January-December 2020 were included. Demographic, clinical features and laboratory data were recorded. DAS28 for disease activity and pain-visual analogue score(VAS) and fatigue-VAS, hospital anxiety-depression(HAD), Pittsburgh Sleep Quality Index(PSQI), and Nottingham Health Profile(NHP) forms for QoL assessment were filled by one-on-one interviews. Patients were grouped to disease activity as: "Low-DAS28 group" and "High-DAS28 group".

Results: In comparison with DAS28, pain-VAS, and fatigue-VAS, and some NHP scores (such as the total score and pain, physical activity, and fatigue subgroup) were significantly higher in the High-DAS28 group than the Low-DAS28 group. However, no difference was found in HAD scores. The sleep disorder subgroup score was higher in the High-DAS28 group but total and other subgroups of the PSQI were similar. Overall DAS28 correlated with NHP total score (0.427, p<0.001), pain-VAS (0.731, p<0.001) and fatigue-VAS (0.505, p<0.001).

Conclusion: To improve the quality of life in rheumatoid arthritis patients is one of the main objectives of treatment. High disease activity seems to be more affecting the patients in terms of pain-VAS, fatigue-VAS, NHP total scores and NHP-pain, NHP physical activity subgroups than other quality of life scales in patients with rheumatoid arthritis.

Keywords: Rheumatoid arthritis, disease activity, quality of life, visual analogue score, sleep quality

Romatoid Artrit Yaşam Kalitesi Ölçeklerinin Hastalık Aktivitesine Göre Değerlendirilmesi

ÖZET

Amaç: Romatoid artrit (RA) hastalarında yaşam kalitesini (QoL) hastalık aktivitesi dışında ağrı, yorgunluk, depresyon, anksiyete ve uyku kalitesi de etkiler. Bu çalışmada RA hastalık aktivitesi ile QoL ölçekleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Bu kesitsel çalışmaya, Ocak-Aralık 2020 tarihleri arasında Ankara Şehir Hastanesi Romatoloji polikliniğine başvuran, ardışık 92 RA hastası dahil edildi. Hastaların demografik verileri, klinik özellikleri ve laboratuvar sonuçları kaydedildi. Hastalık aktivitesini değerlendirmek için DAS28, QoL değerlendirmek için ise ağrı-görsel analog skoru (VAS), yorgunluk-VAS, hastane anksiyete depresyonu(HAD), Pittsburgh Uyku Kalitesi İndeksi (PSQI) ve Nottingham Sağlık Profili (NHP) ölçekleri birebir hasta vizitinde doldurulmuştur. RA hastaları hastalık aktivitesine göre "Düşük-DAS28 grubu" ve "Yüksek-DAS28" olarak olarak gruplandırıldı.

Sonuçlar: Düşük-DAS28 ve Yüksek-DAS-28 gruplarının karşılaştırılmasında, ağrı-VAS, yorgunluk-VAS ve bazı NHP skorları (toplam skor ve ağrı, fiziksel aktivite ve yorgunluk alt grup skorları), Yüksek-DAS28 grubunda istatiksel anlamlı olarak daha yüksekti. Ancak HAD skorları her 2 grupta benzerdi. PSQI uyku bozukluğu altgrup skoru Yüksek-DAS28 grubunda daha yüksekti fakat PSQI total skor ve diğer alt grup skorları skorları her 2 grupta benzerdi. Toplam DAS28 skoru ile NHP toplam (0,427, p<0,001), ağrı-VAS (0,731, p<0,001) ve yorgunluk-VAS (0,505, p<0,001) skorları birbiri ile koreleydi.

Tartışma: Romatoid artritli hastalarda yaşam kalitesini iyileştirmek tedavinin temel amaçlarından biridir. Romatoid artrit hastalarında yüksek hastalık aktivitesinin ağrı-VAS, yorgunluk-VAS, NHP toplam skor ile NHP-ağrı ve NHP fiziksel aktivite alt grup skorları üzerine etkisi diğer QoL ölçekleri ve alt gruplarından daha fazladır.

Anahtar Kelimeler: Görsel analog skoru, hastalık aktivitesi, romatoid artrit, uyku kalitesi, yaşam kalitesi

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Rheumatoid arthritis (RA) is a multisystemic, inflammatory chronic articular disease whose extra-articular organ involvements may be seen on disease course. RA prevalence is 0.5-1%(1), more in women than men (2). Chronic inflammation in RA also causes morbidities in addition to disease activity, and all of these affect quality of life. In the course of RA, disease activity may progress with remissions and exacerbations. Although there are many different assessment scales, disease activity is frequently evaluated with The Disease Activity Score-28 (DAS28) score in the studies (3). DAS28 is very useful for both RA disease activity assessment and follow-up.

As in all chronic diseases, it is important to assess the quality of life in RA. Pain, fatigue, anxiety, depression and deterioration in sleep quality are among the causes affecting the quality of life in RA. Although there are diverse methods, quality of life may be evaluated with both general and specific scale in RA disease. For this purpose, pain-in-Visual Analogue Scale (VAS), fatigue-VAS (4), Hospital Anxiety and Depression (HAD) Scale (5), Nottingham Health Profile (NHP) (6, 7), and Pittsburgh Sleep Quality Index (PSQI) (8) scales are frequently used to evaluate quality of life in patients with RA. The number of tender-swollen joints and elevated acute phase markers may also be associated with all these quality of life scales (9, 10).

In this study, we have evaluated the association among disease activity and quality of life scales in RA patients.

MATERIALS AND METHODS

A total of 92 consecutive RA patients who applied to the Ankara City Hospital rheumatology outpatients clinic between January-December 2020 were included into our cross-sectional study. Diagnoses of patients with RA met the 2010 American College of Rheumatology classification criteria (11). Patients under the age of 18, with mental illness and pregnancy were excluded. The patients were interviewed face to face, their anamnesis was taken, and physical examinations were performed. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies which were assessed in routine outpatient clinic visits were recorded. Disease activity of RA was scored with the DAS28 score. DAS28 score is defined as remission for ≤2.6, low disease activity for 2.6-3.2, moderate disease activity for 3.2- 5.1, and high disease activity for ≥5.1 . Patients with DAS28 score in remission or low disease activity were grouped as "Low DAS28 group" and those with

moderate and/or high disease activity were grouped as "High DAS28 group".

Pain-VAS, fatigue-VAS, HAD, NHP, and PSQI scales were administered to the patients to assess their quality of life. Pain-VAS and fatigue-VAS scores between 0-10 were marked on standard scales by the patients. The HAD anxiety scale was used to measure anxiety levels, and scores of ≥11 and above were considered significant in terms of the presence of anxiety. The HAD depression scale was used to measure depression levels, and scores of ≥8 and above were considered significant. Scores of 5 and above in PSQI were considered significant for poor sleep quality. In the NHP, evaluation was made with a maximum of 100 points in each subgroup in 6 subgroup inquiries. A high score meant that the patients' quality of life was poor. The presence of anxiety and depression was evaluated both as a percentage and a score, separately. Both the total score and the subgroup scores were compared in the NHP and PSQI scales (Table 2). The study was approved by the ethics committee of Ankara City Hospital (30.01.2020-E-kurul-E1-19-205).

Statistical analysis was performed using Statistical Product and Service Solutions 24.0 (IBM Corp., Armonk, NY, USA). The conformity of the variables to the normal distribution was examined with histogram, probability graphs and Shapiro-Wilk test. The χ^2 test was used to compare categorical variables. The categorical variables were defined as percentages, the continuous datas as mean±standard deviation (SD) or median with interquartile range (IQR). Mann-Whitney U or Student t test was used to compare continuous variables. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. A p value of below 0.05 was considered statistically significant.

RESULTS

A total of 92 RA patients included in this study, 68 (74%) were female and the mean age was 57.9±13.4 years. Of the 14% patients were smokers and 69% had at least one comorbidity. The mean±SD DAS28 score was 3.3±1.4, the median Pain-VAS score was 4 (IQR:5), and the fatigue-VAS score was 5 (IQR:8).

When the patients were compared according to DAS-28 scores, 48% (n=44) were in the Low-DAS28 group and 52% (n=48) were in the High-DAS28 group. In Table-1, the general and laboratory findings of all RA patients and

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both groups are given, separately. Age, female gender, body mass index, frequency of patients with at least one comorbidity and smoking were higher in the High-DAS28 group than in the Low-DAS28 group. In both groups, the frequency of RA patients for more than 5 years was around 80%, and there was no difference between RF and CCP positivity (Table 1).

The comparison of the groups in terms of the quality of life scales was shown in Table 2. In this assessment, the median pain-VAS and fatigue-VAS scores were higher in the High-DAS28 group than in the Low-DAS28 group. While anxiety and depression were found to be 10.9% and 15.2%, respectively, in the entire RA group; there was no difference between the groups in terms of the presence of HAD-anxiety, HAD-depression and their total scores. In the NSP scoring, which is another scale in which we evaluate the quality of life, the median total score was higher in the High-DAS28 group than the Low-DAS28 group. In the NHP subgroup analysis, NHP-pain, NHP-physical activity and NHP-fatigue scores were statistically higher in the High-DAS28 group. In the PSQI scoring, in which we evaluated the sleep quality, we found that the sleep quality index was poor in 34.8% of all patients. No statistically significant difference was found in terms of PSQI subgroups when the patients with RA were compared according to their DAS-28 levels, except for the median PSQI-sleep disorder (Table 2).

Overall DAS28 disease activity correlated, in the expected directions, with NHP total score (Spearman's rho = 0.427, p < 0.001), pain-VAS (0.731, p < 0.001) and fatigue-VAS (0.505, p < 0.001). However, there was no correlation between the disease activity and PSQI total score, HAD-anxiety and HAD-depression.

DISCUSSION

In this study, we evaluated the associations with disease activity in RA patients and the quality of life parameters such as sleep quality, quality of life, pain, fatigue, anxiety, and depression. As expected, we found that increased disease activity had a negative impact on pain-VAS, fatigue-VAS scores. In addition to these, the NHP-pain, NHP physical activity was higher in the High DAS28 group. However, there was no relationship between disease activity and PSQI total score, and most PSQI subgroups except for the sleep disorder subgroup.

Table 1. Demographic, clinical and laboratory characteristics of the rheumatoid arthritis patients between the Low DAS28 and High DAS28 groups

	All patients n=92	Low DAS28 Group n=44	High DAS28 Group n=48	P
Age, year (mean ± SD)	57.9±13.4	55.3±13.9	61.8±12.7	**0.020**
Female, n (%)	68 (73.9)	26 (59.1)	42 (87.5)	**0.002**
Smoking, n (%)	13 (14.1)	11 (25.0)	2 (4.2)	**0.004**
Married, n (%)	83 (90.2)	39 (88.6)	44 (91.7)	0.625
Body mass index, kg/m² (mean ± SD)	28.1± 4.8	27.1±4.3	29.3±5.1	**0.027**
Rheumatoid arthritis disease duration > 5 years	73 (79.3)	35 (79.5)	38 (79.2)	0.964
Lives with his/her family, n (%)	88 (95.7)	42 (95.5)	46 (95.8)	0.929
Education level≤ Primary education,n (%)	67 (72.8)	30 (68.2)	37 (77.1)	0.093
At least one comorbid disease, n (%)	63 (68.5)	22 (50.0)	41 (85.4)	**<0.0001**
RF positivity, n (%)	61 (73.5)	29 (72.5)	32 (74.4)	0.843
Anti-CCP positivity, n (%)	45 (54.2)	19 (47.5)	26 (60.5)	0.236
CRP, mg/dL, median (IQR)	6 (10)	6 (6.5)	7 (10.0)	0.170
ESR, mm/h, median (IQR)	20 (15)	17 (19)	23 (17)	**0.009**
Pain-VAS, median (IQR)	4 (5)	0 (3)	5 (4)	**<0.0001**
Fatigue-VAS, median (IQR)	5 (8)	2 (5.3)	5 (5)	**<0.0001**
Precision joint count, median (IQR)	2 (4)	1.5 (2)	4 (6)	**<0.0001**
Number of swollen joints, median (IQR)	0 (0)	0 (0)	0 (0)	0.058

DAS28; Disease activity score-28, RF; Rheumatoid factor, anti-CCP; anti-cyclic citrullinated peptide, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, VAS; Visual Analog Scale

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Table 2. Comparisons of pain, fatigue VAS, HAD anxiety and depression, NHP and PSQI scores of the rheumatoid arthritis patients between the Low DAS28 and High DAS28 groups	Low DAS28 Group n=44	High DAS28 Group n=48	p
Pain-VAS, median (IQR)	0 (3)	5 (4)	**<0.0001**
Fatigue-VAS, median (IQR)	2 (5.3)	5 (5)	**<0.0001**
Anxiety, n (%)	3 (6.8)	7 (14.6)	0.232
HAD-Anxiety score, median (IQR)	1.5 (3)	2 (5.7)	0.289
Depression, n (%)	5 (11.4)	9 (18.8)	0.324
HAD-Depression score, median (IQR)	1 (3)	2 (6)	0.196
NHP-Pain score, median (IQR)	0 (87)	100 (96)	**<0.0001**
NHP-Physical activity score, median (IQR)	0 (100)	100 (100)	**<0.0001**
NHP-Fatigue score, median (IQR)	65 (100)	100 (0)	**0.001**
NHP-Sleep score, median (IQR)	0 (0)	0 (0)	0.270
NHP-Social isolation score, median (IQR)	0 (0)	0 (0)	0.296
NHP-Emotional reaction score, median (IQR)	0 (0)	0 (0)	0.093
NHP-Total, median (IQR)	100 (202)	300 (100)	**<0.0001**
PSQI poor sleep quality,n (%)	13 (29.5)	19 (39.6)	0.315
PSQI-Total, median (IQR)	3 (4)	4 (5)	0.158
PSQI-Subjective sleep, median (IQR)	0 (0)	0 (0)	0.810
PSQI-Sleep latency, median (IQR)	1 (2)	1 (2)	0.323
PSQI-Sleep time, median (IQR)	0 (1)	0 (1)	0.818
PSQI-Sleep Efficiency, median (IQR)	0 (0)	0 (1)	0.766
PSQI-Sleep Disorder, median (IQR)	0 (0)	0 (0)	**0.032**
PSQI-Sleeping pill, median (IQR)	0 (0)	0 (1)	0.109
PSQI-Daytime Dysfunction, median (IQR)	0 (2)	0 (2)	0.503

DAS28; Disease activity score 28, VAS; Visual analog scale, HAD; Hospital Anxiety and Depression Scale, NHP; Nottingam Health Profile, PSQI; Pittsburgh Sleep Quality Index

Sleep disturbance could be accompanied to 50-70% of RA patients, and this rate is two-three times higher than in the normal population (12, 13). In fact, the frequency of sleep disturbance was found to be 80% in two studies conducted in Greece and Brazil (14, 15). In our study, sleep disturbance in our RA patients was found to be less than the studies in the literature (34.8%). Differences such as ethnicity, smoking habits, consumption of alcohol, sample size of the study populations, differences in treatment protocols and the kind of scales which evaluate the sleep quality/disturbance may have caused the lower frequency of sleep disorder in our study than literature.

In the literature, mostly, increased disease activity in RA had a negative effect on the sleep quality (14-18). Conversely, some studies found no association between sleep quality and disease activity in RA, like our findings (19, 20). Loppenthin et al. also found that no significant association between disease activity and pain or sleep quality, but mental and physical fatigue was associated with sleep quality in RA patients. Apart from the disease activity, increased proinflammatory cytokines in RA have been found to lead to a decrease in sleep quality, so it was hypothesized that the increased cytokine levels may not be correlated with the DAS28 scores. (21, 22). Another possibility was that sleep quality assessment was not evaluated by objective methods such as polysomnography and multiple sleep latency testing (19). These hypotheses may be valid for our results as to why we could not find a correlation between disease activity and sleep quality.

Pain, fatigue, depression, and sleep quality impairment are known symptoms of RA and they are interrelated factors to each other. (9). For example, pain may affect sleep quality directly or indirectly by increasing depression (10). Loppenthin et al. was found general and mental fatigue were independent markers affecting poor sleep quality in patients with RA. These findings were also associated with the association of depression and fatigue (19). All these factors may lead to deterioration in quality of life in patients with RA (10).

In our study, there was no difference in PSQI total score between RA disease activity and sleep quality. No statistically significant association was found among PSQI subgroups and RA disease activity, except for the PSQI-sleep disorder subgroup. However, we did not think that this difference was clinically significant. In studies involving more patients, the relationship between PSQI total

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score and subgroups and RA disease activity should be evaluated.

The main limitations of our study are the lack of a control group due to its cross-sectional design. A limited number of patients was also a major limitation of this study. Another limitation of our study is that no evaluation was made in our group in terms of fibromyalgia, which can be seen frequently in RA patients. The absence of some RA-specific scales, health assessment questionnaire (HAQ) and other QoL assessments was another limitation of our study.

In conclusion, pain-VAS, fatigue-VAS and NHP total score and NHP-pain, NHP physical activity subgroup scores from quality of life scales were higher in patients with high-disease activity RA patients than those RA patients with low-disease activity. PSQI-Sleep quality, anxiety and depression scores were not different according to RA disease activity. Improving the quality of life in RA patients is one of the main goals of treatment. Therefore, while evaluating the success of treatment, besides the disease activity parameter, we should also consider the factors of sleep quality, pain, fatigue, anxiety and depression. According to our findings, disease activity is primarily associated with pain, fatigue, and physical activity. Finally, prospective studies with larger numbers of patients are needed to achieve more valid results.

All authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Effect of D-Ribose on Fusobacterium Nucleatum Planktonic Proliferation and Biofilm Maturation

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ABSTRACT

Purpose: Periodontopathogenic biofilm structure is one of the most important factors in the etiology of inflammatory periodontal diseases. Quorum Sensing inhibitors (QSi) can inhibit biofilm development/maturation by inhibiting bacterial communication mechanism. In this study, we examined the effects of D-ribose (QSi) on the planktonic growth and bio. film formation characteristics of *Fusobacterium nucleatum*, an important periodontopathogenic species that has a binding function on early and late colonization types for the development of periodontopathogenic biofilm.

Methods: The strain of *F. nucleatum* (ATCC 25586) and two clinical isolated strains (AHN 9910 and AHN 9508) were used in all tests. Planktonic proliferation (measured as colony forming units) and established biofilm tests (measured as total biofilm mass) were performed in the presence of 50mM D-ribose.

Results: In planktonic growth tests, statistically significant increase was observed for *F. nucleatum* ATCC 25586 and AHN 9508 strains (p<0.05). In established biofilm tests, a mean-based decrease was observed for all species, but a statistically significant difference was found only for *F. nucleatum* AHN 9910.

Conclusions: The fact that the presence of D-ribose can increase the planktonic growth of *F. nucleatum* and its inhibitory effect on biofilm development shows that it may have an adverse effect on biofilm development by disrupting the Quorum-Sensing system.

Keywords: Quorum Sensing, Fusobacterium Nucleatum, Periodontitis, Biofilm

D-Riboz'un Fusobacterium Nucleatum'un Planktonik Çoğalması ve Biyofilm Olgunlaşması Üzerine Etkisi

ÖZET

Amaç: İltihabi periodontal hastalıkların etiyolojisinde periodontopatojenik biyofilm yapısı ana faktörler arasında yer almaktadır. Quorum Sensing inhibitörleri (QSi) bakteriyel haberleşme mekanizmasını inhibe ederek biyofilm gelişimini/olgunlaşmasını engelleyebilmektedir. Biz çalışmamızda D-riboz (QSi) varlığının periodontopatojenik biyofilmin gelişiminde erken ve geç dönem kolonizasyon türlerini bağlayıcı etkiye sahip önemli bir periodontopatojen tür olan Fusobacterium nucleatum'un planktonik çoğalma ve biyofilm oluşturma özellikleri üzerindeki etkilerini araştırdık.

Yöntemler: Tüm testlerde F. nucleatum'un tip suşu (ATCC 25586) ve iki klinik izole suşu (AHN 9910 ve AHN 9508) kullanıldı. Planktonik çoğalma (koloni oluşturan birim olarak ölçüldü) ve yerleşmiş biyofilm testleri (toplam biyofilm kitlesi olarak ölçüldü) 50mM D-riboz varlığında gerçekleştirildi.

Bulgular: Planktonik çoğalma testlerinde 50mM D-Riboz varlığında tüm suşlar için ortalama bazlı artış gözlenmesine rağmen istatistiksel anlamlı artış F. nucleatum ATCC 25586 ve AHN 9508 suşlarında bulundu (p<0.05). Yerleşmiş biyofilm testlerinde tüm türler için ortalama bazlı azalma gözlenmekle birlikte istatistiksel anlamlı farklılık yalnızca F. nucleatum AHN 9910 suşunda bulundu.

Sonuç: D-riboz varlığının F. nucleatum'un planktonik çoğalmasını artırabilmesi ve biyofilm gelişiminde neden olduğu inhibe edici etki Quorum-Sensing sistemini bozarak biyofilm gelişiminde olumsuz etki yaratabileceğini göstermektedir.

Anahtar Kelimeler: Quorum Sensing, Fusobacterium Nucleatum, Periodontitis, Biyofilm

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Periodontitis is a bacterial disease characterized by inflammation affecting the tissues around the tooth. Considering the periodontal diseases in terms of etiology, the biofilm structure with predominantly anaerobic gram-negative rods is the main factor in this regard (1,2). *F. nucleatum* is a gram-negative species that increases in deep periodontal pockets with a negative health status, which helps the periodontopathogenic biofilm to establish a link between late and early colonization types and accelerates the transition of the biofilm to pathogenicity. *F. nucleatum* can also invade epithelial tissue and cause increased secretion of matrix metalloproteinases (MMPs) in the host tissue; this allows it to play a role in tissue destruction (2,3,5).

Biofilm can be described as self-organizing microbial communities that adhere to living and non-living surfaces and produce extracellular polymeric matrix (4). This organized structure allows bacteria to survive in an environment under stress, to increase their colonization characteristics, and to increase the number of pathogenic bacteria (5,6).

Quorum Sensing (QS) system, which has a major role in biofilm activity, contributes to the establishment of the biofilm order and maintenance of its continuity. Bacteria in the biofilm maintain their communication with each other with the help of the QS system. The LuxS/AI-2 (QS) system can be observed extensively for both gram-negative and gram-positive bacteria. The signal molecule Autoinducer-2 (AI-2) is acknowledged as a general communication language for intra-species and inter-species communication (7,8).

QS inhibitors (QSi) have the potential to significantly reduce bacterial virulence by preventing biofilm formation. Therefore, it can be an important factor for controlling bacterial infection; moreover, they can be an alternative for antibiotics due to this effect (9,10). Ribose components, which are also included in the QS inhibitors, may have an effect on the QS system without toxic effects (11). Since ribose is structurally similar to AI-2, it is thought that it creates an inhibitory effect by creating competition with AI-2 within the biofilm QS system. (12, 13, 14, 15). However, data about the effects of QS inhibitors on periodontopathogenic bacteria and the mechanism of inhibition is still quite limited in the literature. Therefore, the purpose of this study is to examine the planktonic growth and biofilm formation ability of *F. nucleatum*, a periodontopathogenic species commonly found in biofilm under both healthy conditions and periodontal disease conditions, in the presence of QSi (D-ribose).

MATERIAL AND METHOD

Bacterial Species and Cultures

The *F. nucleatum* type strain (ssp. *nucleatum* ATCC 25586) and two clinical isolated strains (ssp. *nucleatum* AHN 9910 and ssp. *nucleatum* AHN 9508) were used in all experiments. Strains were obtained from the Finnish National Institute for Health and Welfare (THL). According to the data from THL database, clinical strain AHN 9508 was isolated from the gingival crevice and clinical strain AHN 9910 was isolated from saliva. Before all experiments, strains were grown on Brucella agars supplemented with Hemin (5mg/l) and vitamin K1 (10mg/l) in anaerobic atmosphere (10% H_2, 5% CO_2, 85% N_2 at 37°C, Whitley A35 Anaerobic Workstation, Don Whitley Scientific®, West Yorkshire, UK) for 5 days. Afterwards, colonies collected from agars with the help of sterile cotton swabs were transferred to Bactotrypton liquid medium supplemented with Saccharose (1%), KH_2PO_4 (25 mM) and $MgSO_4$ (4 mM). In order to ensure planktonic growth in the liquid medium, these colonies were kept in anaerobic conditions for 2 days, and the optical densities of all strains were adjusted to 0.5 (OD) at 490 nm, and they were prepared for the tests. It was assumed that this value was equivalent to 4×10^7 CFU/ml (16, 17).

Preparation of QSi Concentration

After commercial purchase of D-ribose (D-(-)-Ribose, Tokyo Chemical Industry®, Tokyo, Japan), it was stored at +4°C until the day of use. D-ribose was prepared as a 200mM stock concentration by dissolving it in liquid medium on the test day in all experiments. In all D-ribose tests, the study groups were diluted with liquid medium to a final concentration of 50mM and the test phase was started afterwards (11, 18).

Planktonic Growth Test

All bacterial strains were set to 0.5 OD (490nm). Control and test groups were prepared in triplicate with a total volume of 200µl. After a 24-hour incubation period under anaerobic conditions, the liquids in eppendorf tubes were diluted for CFU analysis and spread on agar with the help of cotton pellets. Colony numbers were recorded by direct counting after 3-5 days of incubation of the agars under anaerobic conditions. Each test was repeated with the same procedure on three different days.

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Covering of 96-Well Plates with Saliva for Stimulation of Biofilm Formation

Saliva was prepared as stock before all experiments. The saliva collected by the primary researcher with the support of paraffin use (Healthy individual, no antibiotic or any drug use in the last 3 months, no smoking) was transferred to a propylene tube and centrifuged at 4°C for 40 minutes at 12,000 g value. Supernatant was collected and transferred to sterile tubes. After the pasteurization process (60° x 30min), it was centrifuged again at 4°C for 40 minutes at 12,000 g value and stored at 4°C until the day of use. The prepared saliva was spread on Brucella agars for sterilization control and incubated for 5 days under aerobic and anaerobic conditions. As a result of sterilization test, no colony formation was observed on Brucella agars.

RESULTS

Planktonic Live Bacteria Growth Results

A statistically significant increase ($p < 0.05$) was found for type strain *F. nucleatum* ATCC 25586 and clinical strain *F. nucleatum* AHN 9508 in the presence of 50mM D-ribose in 24-hour planktonic growth tests. Although mean-based increase was observed for *F. nucleatum* AHN9910, no statistically significant difference ($p > 0.05$) was found for this strain (Figure 1).

Biofilm Formation (Established) Results

In all established biofilm tests, a decrease in mean-based biofilm mass was observed for all strains of *F. nucleatum*. However, statistically significant decrease in biofilm was found only for clinical strain *F. nucleatum* AHN 9910 among the strains ($p < 0.05$) (Figure 2).

DISCUSSION

Pathogenic biofilm structure plays the leading role in the pathogenesis of inflammatory periodontal diseases. *F. nucleatum*, which is in a complex biofilm structure, is a gram-negative anaerobic bacteria species that acts as a bridge between early colonization species and late colonization species and has important effects on the pathogenesis of the disease. Autoinducer-2 (AI-2) signals, one of the communication signals of bacteria, are used by both gram-negative and gram-positive species within the Quorum Sensing system. AI-2 signaling system is also used by *F. nucleatum* (18).
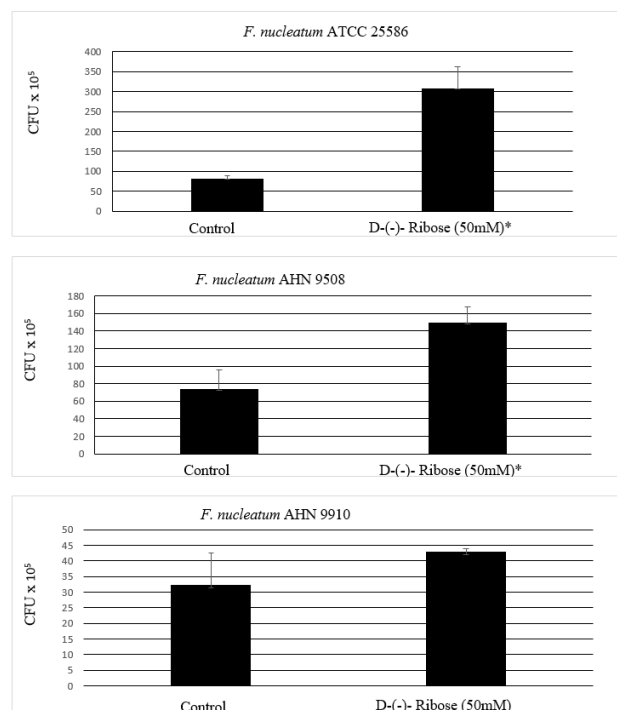
Figure:1 Planktonic growth of three F. nucleatum strains in the D-(-)-Ribose concentration of 50mM. Asterix shows a significant difference compared to control ($p < 0.05$)
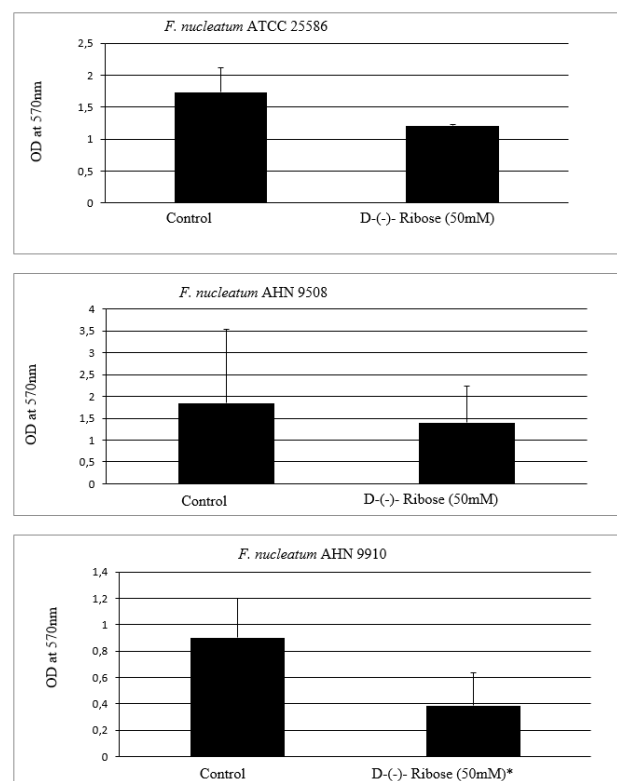
Figure:2 Biofilm formation (established) of three F. nucleatum strains in the D-(-)-Ribose concentration of 50mM. Asteriks shows a significant difference compared to control ($p < 0.05$)

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DISCUSSION

Pathogenic biofilm structure plays the leading role in the pathogenesis of inflammatory periodontal diseases. *F. nucleatum*, which is in a complex biofilm structure, is a gram-negative anaerobic bacteria species that acts as a bridge between early colonization species and late colonization species and has important effects on the pathogenesis of the disease. Autoinducer-2 (AI-2) signals, one of the communication signals of bacteria, are used by both gram-negative and gram-positive species within the Quorum Sensing system. AI-2 signaling system is also used by *F. nucleatum* (18).

D-ribose, which is one of the Quorum sensing inhibitors, can create inhibition within the QS system by competing with AI-2 signals. One of the most important advantages of D-ribose is that it has minimal toxic side effects (11, 21, 22). Among quorum sensing inhibitors, another frequently used compound in in vitro biofilm studies is Furanone. However, it has been shown that Furanone can have potential toxicity on fibroblasts and it was considered that Furanone compounds may have harmful effects in treatments for humans (19, 20). Therefore, we decided to use D-ribose in the present study.

In this study, the effect of different strains of *F. nucleatum*, which has an important role in the pathogenesis of inflammatory periodontal diseases in the presence of D-ribose, on the mass-based experimental biofilm structure was observed for the first time.

Type strain *F. nucleatum* ATCC 25586 and clinical strains (*F. nucleatum* AHN 9508 and AHN 9910) isolated and stocked from clinical cases were used in order to observe behavioral variances among different strains of the same species in experimental biofilm mass analyzes and planktonic growth tests of *F. nucleatum* (17). We determined the D-ribose concentration we used in our experiments as 50mM, which has been proved to be effective in QS inhibition based on the current literature (13, 18).

Analysis of living bacteria count with CFU, which has also been used in other studies, is acknowledged as the gold standard in the literature (3, 17, 23). We observed a statistically significant increase in *F. nucleatum* ATCC 25586 and *F. nucleatum* AHN 9508 strains in the presence of D-ribose as a result of the planktonic growth tests performed with CFU. For *F. nucleatum* AHN 9910 strain, on the other hand, we did not observe a statistically significant difference, although there was a mean-based increase. D-ribose, which

is also included in the digestive system, may play a role as a carbon source for the bacterial microbiota (24, 25). Although ribose uptake and metabolic phosphorylation have been detected in many studies in the literature for many bacterial species, the presence of ribose in the environment may also contribute to the increase in bacterial growth (24, 26). We think that D-ribose, a carbon-derived sugar that is abundant in nature, triggers bacterial growth due to an increase in its metabolic use.

Its biofilm forming ability is very important among the virulence factors of bacteria. Therefore, factors that can inhibit periodontopathogenic biofilm formation are important in terms of the occurrence of periodontal diseases and prevention of the progression of diseases (27, 28). In this study, we decided to apply biofilm formation tests, which were successfully applied in other studies in the literature, for single biofilm tests of *F. nucleatum* (17, 28).

Although mean-based decrease was observed for all *F. nucleatum* strains in established biofilm tests, statistically significant difference was found only for *F. nucleatum* AHN 9910 strain. In the studies in the literature, there are results showing that there may be biofilm inhibition in the presence of D-ribose (11, 18). In the study of Jang et al., it was shown that multiple biofilms formed with *Tannerella forsythia*, *Treponema denticola* and *Porphyromonas gingivalis*, which are among the important periodontopathogenic bacteria, can be inhibited by D-ribose (18). In the study of Liu L. et al., it was shown that D-ribose can exert dose-dependent antibiofilm activity on *Lactobacillus paraplantarum*, a gram-positive microaerophilic bacterium (11). In the study of Jang et al., it was observed that D-ribose can inhibit dual-biofilm formation using *Streptococcus gordonii*, which is a life-threatening oral bacterial species that can cause infective endocarditis and can coaggregate strongly with *F. nucleatum* (22).

Studies examining the clinical effectiveness of D-ribose have also shown that it can reduce periodontal damage. For example, Ben Amara et al. (29) found in their in-vivo study that the presence of 50mM D-ribose may reduce periodontal damage. In the same study it was also found that the total bacterial count was significantly reduced in the group treated with D-ribose. In the study of Cho et al. (13), they found that the application of D-ribose may reduce periodontal bone destruction.

We think that the presence of D-ribose may have an inhibitory effect on the biofilm formation capacity, which

is an important virulence factor for the occurrence and progression of periodontal diseases. The fact that in the presence of D-ribose can cause an increase in the planktonic growth of *F. nucleatum* and can decrease its biofilm formation capacity, it strengthens the idea that it can disrupt the Quorum Sensing system.

Treatment strategies of periodontopathogenic biofilm-mediated diseases focus on eradication of biofilm by scaling and root planing procedures and sometimes followed by adjunctive use of antiseptics and/or antibiotics. However, chlorhexidine is characterized by discoloration of teeth, bitter taste, and more rarely, mucosal irritation. On the other hand, antibiotics can have various systemic side effects, as well as antibiotic resistance can develop after prolonged use (1, 30). Considering the results of this study and literature data together, D-ribose could be considered as promising alternatives for the adjunctive treatment of biofilm-associated infections. Clinical studies including toxicity analyses as well as multiple biofilm studies with multi-species are required in order to fully explain the effects of Quorum Sensing inhibitors on periodontopathogenic biofilm.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   Physical Medicine and Rehabilitation / Fiziksel Tıp ve Rehabilitasyon

Investigation of Cognitive, Psychological and Physical Factors Affecting Academic Performance of University Students by Principal Component Analysis During the Covid-19 Pandemic

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ABSTRACT

Purpose: The Covid-19 Pandemic has significantly affected the physical activity levels, psychosocial status, cognitive skills, and academic performances of university students in the health field. The aim of this study is to examine the factors affecting the academic performance of university students with principal component analysis.

Methods: 151 University students (aged 21.83±1.88 years; 125 female, 26 male) participated in the study. The CogniFit Cognitive Assessment Program, the International Physical Activity Questionnaire Short Form, Academic Self-Efficacy Scale, Pittsburg Sleep Quality Index, Beck Depression Inventory, and Beck Anxiety Inventory were administered to the students via the Google Form. The Principal Component Analysis was used to evaluate the data.

Results: The Principal Component Analysis (PCA) yielded three principal components (PC) that together account for 93% of the variation in the data set and represent new and distinct patterns. Thus, 11 variables affecting the subject were reduced to three components. These 3 components include all the cognitive functions evaluated. In addition, sleep and depression variables are also included.

Conclusion: The cognitive, emotional, and physical factors affecting the academic performance of university students have been systematically classified and made easier to prioritize and understand. In this way, the parameters that need improvement were laid out.

Keywords: University students, principal component analysis, academic performance, cognitive functions, pandemic

Covid-19 Pandemisi Sürecinde Üniversite Öğrencilerinin Akademik Performansını Etkileyen Bilişsel, Psikolojik ve Fiziksel Faktörlerin Temel Bileşenler Analizi İle İncelenmesi

ÖZET

Amaç: Covid-19 Pandemisi, sağlık alanında eğitim görmekte olan üniversite öğrencilerinin fiziksel aktivite düzeylerini, psikososyal durumlarını, bilişsel becerilerini ve akademik performanslarını önemli ölçüde etkilemiştir. Bu çalışmanın amacı, üniversite öğrencilerinin akademik performansını etkileyen faktörleri temel bileşenler analizi ile incelemektir.

Yöntem: Araştırmaya 151 üniversite öğrencisi (21.83±1.88 yıl; 125 kadın, 26 erkek) katılmıştır. Öğrencilere Google Formu aracılığıyla CogniFit Bilişsel Değerlendirme Programı, Uluslararası Fiziksel Aktivite Anketi Kısa Formu, Akademik Öz-yeterlik Ölçeği, Pittsburg Uyku Kalitesi İndeksi, Beck Depresyon Envanteri ve Beck Anksiyete Envanteri uygulanmıştır. Verileri değerlendirmek için Temel Bileşen Analizi kullanılmıştır.

Bulgular: Temel Bileşen Analizi, veri setindeki varyasyonun %93'ünü oluşturan ve yeni ve farklı modelleri temsil eden üç temel bileşen (PC) sunmuştur. Böylece konuyu etkileyen 11 farklı değişken üç bileşene indirgenmiştir. Bu 3 bileşen, değerlendirilen tüm bilişsel işlevleri içermektedir. Ayrıca uyku ve depresyon değişkenleri de yer almaktadır.

Sonuç: Araştırmanın sonunda üniversite öğrencilerinin akademik performansını etkileyen bilişsel, duygusal ve fiziksel faktörler sistematik olarak sınıflandırılmış, önceliklendirilmesi ve anlaşılması kolaylaştırılmıştır. Bu şekilde sağlık eğitimi sürecinde iyileştirilmesi gereken parametreler ortaya konmuştur.

Anahtar Kelimeler: Üniversite öğrencileri, temel bileşen analizi, akademik performans, bilişsel işlevler, pandemi

Investigation of the cognitive, psychological, and physical factors affecting the academic success of students during the pandemic is important in terms of effective management of this process. Due to the long isolation period, the relationship between students' stress, anxiety levels, cognitive function, and academic achievement attracts great attention during this period. Determining the factors affecting students' cognitive status and taking necessary precautions, especially making learning-teaching processes more efficient, will be very beneficial for academic success (1).

The pandemic leads students to a sedentary lifestyle and may negatively affect physical performance, increasing disease and health problems. While physical activity is known to improve cognitive functions, research continues on the consistency and magnitude of its effects, the cognitive areas most affected, and the parameters necessary to achieve the greatest improvements (2). In addition, the increase in the time spent at home with the online education process can cause many problems for university students. While this situation negatively affects the sleep quality of the students, it can increase their depression and anxiety levels (3). Physical activity has been shown to have many positive effects on the body in general. It regulates blood pressure and prevents the formation of hypercholesterolemia, increases bone and mineral density, prevents obesity and has positive effects on mental health problems like depression, and anxiety. In addition, it has been reported that students who do physical activity improve self-confidence, self-esteem, and feelings of competence, increase their energy and reduce the feeling of fatigue. However, studies on the effects of physical activity on cognitive functions such as attention, learning, and memory are limited (4).

"CogniFit" (CogniFit, Inc.), one of the current cognitive assessment technologies, contains validated tasks for the assessment of 23 cognitive skills. The test is used as a professional tool to help detect cognitive changes using neuropsychological assessments. It also provides the opportunity to monitor the development of cognitive skills. At the end of the cognitive assessment, different insights about the cognition of the students are gained and it is determined which ones are strong and which ones need training (5).

Pandemic has been an important process affecting university students' physical activity levels, psychosocial status, cognitive skills, and academic success. CogniFit and similar applications have started to be used in the evaluations, and such evaluations have gained great importance in this process where face-to-face applications cannot be made together with the pandemic process (6).

This study aims to analyze the factors affecting the academic performance of university students that have been systematically classified and made easier to prioritize and understand. For this purpose, we have used Principal Component Analysis (PCA). While there are many possible variables that can affect students' academic performance, this means a lot of data. Thus, we have reduced a large number of variables to main components. In addition, cognitive functions in our research were carried out through a current technological mobile application. Thus, this technology-based research, it is aimed to evaluate and systematize the factors affecting the academic performance of students during the pandemic with the application of PCA, which is an advanced statistical method.

MATERIALS AND METHODS

This study was carried out on volunteer university students at Biruni University Faculty of Health Sciences between April 2021 and July 2021. Ethics committee approval was received from Biruni University Ethics Committee, dated 09/04/2021, number 2021/50-33.

Based on the literature, considering sleep quality and depression data, the minimum sample size was calculated as 136 people at 95% power (6). Oral and written consent was requested from the participants.

The inclusion criteria are to be a university student, to be between the ages of 18-25, to attend online classes regularly during the pandemic and to be able to read, write and understand Turkish. Exclusion criteria are the presence of orthopedic, neurological, psychiatric, and vision-hearing problems that would prevent participation in the study.

Demographic information form, CogniFit Cognitive Assessment Application, Academic Self-Efficacy Scale (ASES), Pittsburg Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were administered to the students. The data relating to the physical activity variable of all students were evaluated with the International Physical Activity Questionnaire Short Form (IPAQ-SF). In addition, the students' grade points averages (GPA) were recorded.

Before the cognitive evaluations, necessary permissions were obtained from the company for the software. Later, a mobile application was installed on all students' mobile phones and the features of the application were introduced. Other questionnaires were prepared on google form and applied to all students online. Thus, all the data received from the students were recorded in a completely virtual environment.

Instruments

General Cognitive Assessment Battery (GCAB) by CogniFit™ is a 40-minute online neuropsychological tool designed to precisely evaluate a wide range of abilities and assess cognitive well-being. Using clinically and scientifically validated online cognitive tasks, GCAB identifies strengths and weaknesses in cognition in children 7+ and adults (5). The CogniFit is designed to evaluate a total of 21 cognitive functions divided into five cognitive domains (attention, memory, coordination, perception, and reasoning). Each objective score is derived from raw scores and weights determined by factor analysis (6). The final score is the measure of the current cognitive strength of different cognitive skills.

A score between 0 - 200; below the average of your age. The score will be shown in red. Cognitive abilities with this score are considered cognitive weaknesses since they will be below what was expected for people of the same age and sex.

A score between 200 - 400; low scores, although within the average. The score will look yellow, since the cognitive abilities with this score will be within what is expected for people of your age and gender, but they are still improvable.

A score between 400 - 600; high scores within the average. The score will be green since the cognitive abilities with these scores will be in good condition with respect to people of the same age and sex.

Score between 600 – 800; cognitive situations above the average. The score will also look green. The cognitive abilities with this score will be considered strengths or cognitive skills since they will be in a better state than the average for people of your same-sex and age (5).

International Physical Activity Questionnaire - Short Form (IPAQ-SF), determines the types of the intensity of physical activity and sitting time. These are considered to estimate total physical activity in MET-min/week (1 MET=3.5 ml/kg/min) and time spent sitting. It consists of open-ended questions that involve individuals remembering the last 7 days of physical activity. Turkish versions of the IPAQ SF is reliable and valid in the assessment of physical activity (7).

The Academic Self-Efficacy Scale (ASES) is the individual's perception of being able to perform a given academic task at a specified level of success. The scale consists of three sub-dimensions: social status, cognitive and technical skills. The scale includes 33 items. While the Cronbach Alpha reliability coefficient was found to be 0.86 for the overall scale, it was found to be 0.88 for the social status, 0.82 for the cognitive practices, and 0.90 for the technical skills dimension (8).

Pittsburgh Sleep Quality Index (PSQI) is an 18-item questionnaire that evaluates sleep quality over 1 month period. The items are divided into 7 component scores: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, medication use, and daytime dysfunction. These items are scored on a four-point Likert scale. The component scores provide a total PSQI score that ranges from 0 to 21, with higher scores meaning lower sleep quality (9).

Beck Depression Inventory (BDI) is a 21-item self-report questionnaire. The items are scored between 0 and 3 according to the severity of the depression. The minimum and maximum scores are 0 and 63. Scoring is as follows, 0-9, no depression; 10-16 mild depression, 17-24 moderate depression, 25 and above severe depression. The scale was adapted into Turkish by Hisli (10).

Beck Anxiety Inventory (BAI) evaluates the frequency of anxiety symptoms experienced by the individual. It is a 21-item tool designed to assess the anxiety level that is applicable to the general population [16]. Each item is rated on a four-point Likert scale ranging from 0 =not at all to 3 =severe. The total score ranged from 0 to 63. A score of 0–7 is defined as normal/minimal anxiety, 8–15 as mild anxiety, 16–25 as moderate anxiety, and 26–63 as severe anxiety (11).

After the data collection process was carried out, the statistical analysis process was started.

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Statistical Analysis

PCA is a multivariate statistics method. It reduces the multidimensionality of a relevant multivariate data set to a small number of independent main components. Each principal component (PC) contains all variable information and new variables created as linear combinations or mixtures of initial variables.

In this study, PCA was conducted on the assessment scores which applied to university students. For the proper use of PCA, the data were tested with Kaiser-Meyer-Olkin (KMO) and Bartlett tests. These tests were used to examine the adequacy of the selected sample and the independence of each variable, respectively. Firstly, components with eigenvalues > 1.0 were considered. Ten components with eigenvalues > 1 were selected.

Two-sided p values were considered statistically significant at p≤0.05. All statistical analyses were carried out by using R software/programming (version 3.6.2 (2019-12-12) – Comprehensive R Archive Network (CRAN) (12).

RESULTS

A total of 151 university students (aged 21.83±1.88 years; 125 female, 26 male) participated in our study. The demographic features of the students are shown in table 1.

As a result of the research, 54 (35%) of the students stated that they slept less than 8 hours, 82 (55%) 8-10 hours, and 15 (10%) slept more than 10 hours.

In terms of academic achievement scores, 50% of the students have an average score between 3 and 4, and 47% have an average score between 2 and 3. This shows that the majority of students were successful in their exams during the pandemic.

Cognifit total score average of the participants is 435.34. This value corresponds to low cognitive risk. When the parameters are analyzed one by one, reasoning, and attention have low scores although within average; memory, coordination and perception have high scores within average (Figure 1).

In terms of depression, the mean value of 13.16 points corresponds to mild depression (Figure 2). When the anxiety values are examined, the value of 15.44 indicates moderate anxiety (Figure 3).

The average total met value is 1390 points, corresponding to minimal assets (category 2).

All assessment scores are shown in table 2.

As a result of the principal component analysis, 3 components were obtained. The first principal component (PC1) has a high variance (72%). These 3 components have a high total variance of 93.41% and are shown in table 3.

Table 1. Demographic features of the participants				
	N	**Percent**	**Mean**	**SD**
Age			21,83	1.88
Gender				
Female	125	82.78		
Male	26	17.22		
BMI			21.81	3.40
Smokers	27	18		
Non-smokers	124	82		
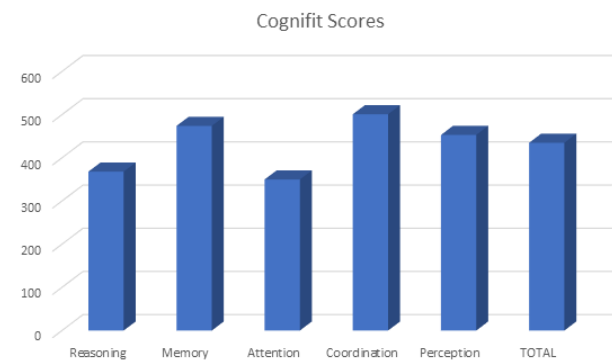
Figure 1. Cognifit scores of the participants
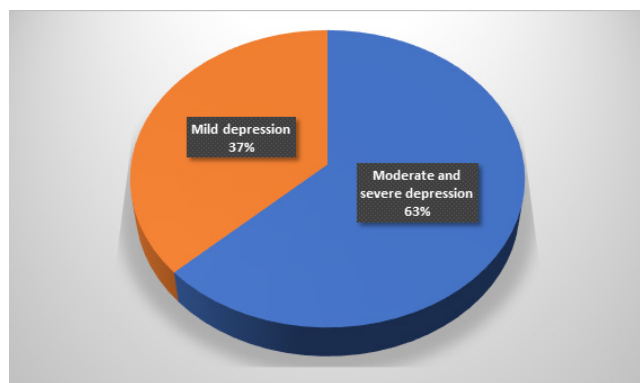
Figure 2. Depression percentages of the participants

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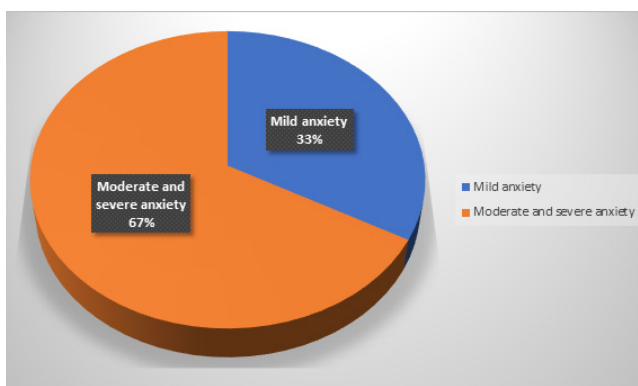
Figure 3. Anxiety percentages of the participants

Table 3. Principal components			
		Principal Components	Variance
1		Physical activity level walking score Attention Coordination Perception	72%
2		Sleep quality Total cognitive level Academic self-efficacy	15%
3		Depression Reasoning Memory	6%

Table 2. Assessment scores and percentages of the participants				
	N	Percent	Mean	SD
GPA	151		2.93	0.46
1.5-2.0	5	3		
2.0-2.5	19	12		
2.5-3.0	53	35		
3.0-3.5	61	41		
3.5-4.0	13	9		
ASES	151		20.28	2.64
COGNIFIT TOTAL	151		435,34	35.52
Reasoning			368,2	19.60
Memory			474,4	23.90
Attention			350,4	38.30
Coordination			501,05	53.03
Perception			453,29	47.06
PSQI	151		5,74	3.33
SLEEP TIME				
<8 hours	54	35		
8-10 hours	82	55		
>10 hours	15	10		
BDI	151		13,16	4.06
BAI	151		15,44	5.14
TOTAL MET	151		1390	201.80

*BMI (Body Mass Index)
*GPA (Grade point average)
*ASES (Academic Self-Efficacy Scale)
*PSQI (Pittsburgh Sleep Quality Index)
*BDI (Beck Depression Inventory)
*BAI (Beck Anxiety Inventory)
*MET (Metabolic equivalent)

PC 1: Physical activity level walking score, attention, coordination and perception (72% variance).

PC 2: Sleep quality, total cognitive level and academic self-efficacy (15% variance)

PC 3: Depression, reasoning and memory variables (6% variance)

As a result of the research, the variables applied to the students were reduced to three basic components including the variables related to each other. Interpretation of the data will be done through these components.

DISCUSSION

In this research, we aimed to analyze the factors affecting the academic performance of university students who receive online education in this process by using the principal component analysis and reducing a large number of variables to basic components. In the COVID-19 pandemic, university educators have been asked to bring all their teaching and assessment activities online in a relatively short time. As a result, all lessons, simulations, applications and evaluations were adapted to the online environment and made available for use. From a student perspective, there has been an opportunity to develop and adopt new skills (13). Thus, it is aimed to obtain more systemic and easily interpretable results. With the analysis made in this context, 3 PCs were determined and a high variance value of 93% was reached.

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In PC1 (%73 variances), the relationship between the walking parameter of physical activity and attention, coordination, and perception, was revealed. When the cognitive evaluation results were examined, it was seen that the total score was above the average (400-600) and that they were in a similar situation to their peers. When the sub-steps of cognitive assessment were examined, it was concluded that while the memory, coordination, and perception parameters scores were still above the average, the reasoning and attention scores were below the average. In terms of physical activity, it is seen that the physical activity levels of the participants are in the minimal active category and walking activity is at the forefront.

Physical activity in young people is an essential part of healthy aging and maintaining cognitive and cardiovascular functions. Regular physical activity is recognized as an essential attribute of students' academic performances. Sports-related activities strengthen the soul and mind and bring creativity. Young people who are not physically active are more likely to adopt other unhealthy behaviors (such as tobacco, alcohol, and drug use), resulting in poor academic performance. Aerobic activity strongly improves performance on tasks involving executive cognitive functions such as planning, programming, inhibition control, and working memory. Students who have improved physical health show higher memory performance.

Previous studies have suggested that physical activity helps achieve better academic performance through increased serotonin secretion, improved cerebral circulation, changes in hormone levels, and increased self-esteem (14). Other researchers have also found a positive correlation between the physical activity level and cognitive functioning, especially the working memory (15, 16).

A moderately significant relationship between physical health and academic performance was found among Nigerian university students. This was also in line with other findings, which showed a positive relationship between physical activity level and academic achievement. Comparably, another researcher found that students who were physically inactive and have lower physical activity levels reported lower academic levels (17, 18).

PC2 revealed the relationship between university students' sleep quality, total cognitive level, and academic self-efficiency variables. Sleep, the variable with the highest variance in this component, is a concept that deserves special attention. It is recommended that young

adults get 8 hours of sleep. However, most young adults sleep less than this period (19). Sleep disturbance is common among university students who live in an environment that promotes sleep reduction due to the burden of academic work and social pursuits. It often causes depression and poor academic performance. Decreased sleep time has been associated with poor academic performance (20-22).

It was observed that 35% of the students included in our study sleep less than 8 hours. Studies show that poor sleep habits have a negative impact on academic performance and mental health complaints. The effect of sleep disturbance on cognitive performance has also been documented previously with a correlation between sleep quality and GPA in university students (23,24). As revealed in our study, sleep and cognitive skills are closely related. High-quality and optimal duration of sleep helps maintain concentration, executive cognitive functions, sensorimotor integration, memory and learning (25). When the GPA values of the students participating in our research were examined, it was seen that 50% of them were very successful and 12% had a sufficient grade point average. In higher education, student selection procedures reduce the variation in intelligence scores, especially in selective faculties. At this level, factors other than intelligence can be important to precisely predicting performance. GPA is the main criterion for post-graduate selection and graduate employment and predicts professional status.

The relationship between cognitive skills and academic self-efficacy in PC2 is also extremely important. The perceived academic self-efficacy and performance are factors that are correlated. Students with high academic self-efficacy displayed more cognitive skills that helped them organize themselves better (26, 27).

Along with depression, reasoning and memory variables, are involved in PC3. During times of enormous uncertainty, such major lifestyle changes are associated with mental health issues such as a higher risk of depression during the pandemic. Depression is a major mental disorder with symptoms such as exaggerated and persistent sadness, cognitive impairments, and a tendency to negative teasing, as well as fatigue and insomnia. It has been shown that about one-fifth of college students suffer from existing mental health problems. In Sweden, between 25% and 50% of students show symptoms of these problems. Mental health problems are the biggest barrier

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to academic performance and can affect students' motivation and concentration (28).

In our study, the mean of depression was found to be 13.13, which indicates the presence of mild depression. The result of the anxiety assessment indicates moderate anxiety with an average value of 15.44. It has been observed that about one-fifth of the students suffer from mental health problems. This population was at high risk of experiencing anxiety, depression, and panic attacks during the pandemic. Depression levels among students reported in recent studies range from 29% to 38%, which may indicate an increase in pandemic-related depressive symptoms among college students in China (29).

Both difficulties concentrating and changes in sleeping habits are associated with depression.

The American College Health Association reported that faced with the pandemic situation, Turkish and American university students, respectively, had a high risk of suffering anxiety, depression, and panic attacks (30).

General threats posed by the pandemic include increased sedentary behavior, mental health effects, and impacts on daily life and work. Students often followed public health advice during the pandemic, but many reported significant negative results regarding academic self-efficacy and mental health status. In order to prepare for the pandemic and similar future crises, online education options should be developed to increase cognitive skills, build resilience and alleviate students' suffering (27, 28).

The individual approach, which takes into account the strengths and weaknesses of each participant, is one of the most important advantages of web-based platforms for cognitive training and screening. We used the CogniFit application, which is a valid cognitive assessment tool, in our research. Thus, we evaluated the young generation, which is intertwined with technology, with a modern method.

It can be predicted that the pandemic will continue for a long time. Technological developments accelerated by this process have also caused the habit of online lessons and meetings to settle. In order to increase students' adaptation to this process, it is of great importance to first find out which factors affect their academic performance and make the necessary improvements. With the PCA method, which we have applied within the scope of our research, these factors have been systematically analyzed. Thus, it has been demonstrated which education parameters should be improved.

In the future, it is planned to carry out preventive and intervention studies by making use of systematic findings that affect the academic achievement of university students. We believe that the transition to the improvement process by taking these factors into account in the university education will be an effective, efficient and practical solution.

Limitations

Considering that the education styles of each department at the university are different, this situation was not fully detailed in our research and only a sample group was formed as students in the field of health sciences. In future studies, having a structure that includes departmental differences will provide more precise results.

DECLARATIONS

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

Ethics Approval

Ethical approval was obtained from Biruni University Non-Interventional Clinical Research Ethics Committee on 09.04.2021, number 2021/50-33.

Permission to Reproduce Material from Other Sources

This article includes no material from other sources.

Authors' Contributions

BÖ: Conceptualization, review and editing, supervision; RA, BB, BÖ: Conceptualization, investigation, Writing–Original Draft; BB: Review and editing, supervision; YÇ: Methodology, statistical analysis; BÖ, RA: Investigation, review and editing.

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Supplementary Data

Rotated Component Matrix[a]			
Variable	**Component**		
	1	**2**	**3**
SEVERE MET	-,001	-,019	,084
AVERAGE MET	-,090	,124	,186
GPA	-,039	,270	,003
DD	-,004	-,062	-,002
USP	-,022	-,042	,028
SD	-,017	-,004	,003
HSA	-,016	,007	,000

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ST	,004	,027	,004
SSQ	-,035	,009	-,018
CLASS	,014	-,017	-,006
SL	-,197	,819	,107
TIB	,057	,001	-,001
GENDER	-,040	-,062	-,039
SITTING MET	-,006	-,092	,014
TOTAL MET	-,021	-,039	,029
BAI	-,011	-,035	-,061
BDI	,037	,011	**-38,04**
REASONING	,007	,050	**82,23**
PSQI	,003	**58,65**	,039
COGNIFIT TOTAL	2,78	**62,51**	23,870
WALKING MET	**79,45**	-7,958	48,609
MEMORY	75,62	1,813	**94,62**
ATTENTION	**90,93**	-3,385	-43,951
COORDINATION	**48,13**	27,412	-32,307
PERCEPTION	**39,91**	6,693	-1,726
ASES	-34,496	**375,5**	-6,069
% of Variance	72,193	15,249	5,969
Cumulative %	72,193	87,442	93,411

*BMI (Body Mass Index)
*GPA (Grade point average)
*ASES (Academic Self-Efficacy Scale)
*PSQI (Pittsburgh Sleep Quality Index)
*BDI (Beck Depression Inventory)
*BAI (Beck Anxiety Inventory)
*MET (Metabolic equivalent)
*SSQ (Subjective Sleep Quality)
*DD (Daytime dysfunction)
*HSA (Habitual sleep activity)
*ST (Sleep Time)
*SL (Sleep Latance)
*SD (Sleep Disorder)
*USP (Use of Sleeping Pills)
*TIB (Time in Bed)

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Geriatrics and Gerontology / Geriatri ve Gerontoloji

Effect of Group Reminiscence Therapy on the Loneliness, Depression and Life Satisfaction of the Elderly in the Nursing Homes

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ABSTRACT

Objective: The study aimed to examine the effect of group reminiscence therapy among elderly people who living nursing homes.

Methods: This randomized controlled trial was performed in two nursing homes in Turkey. A total of 76 elderly recruited the intervention group (n= 37) and the control group (n=39). The intervention group received reminiscence therapy in the form of group sessions lasting 30-45 minutes once a week for six weeks. The control group had no application. Data were collected using a socio-demographic form, the Loneliness Scale, Beck Depression Scale, and Life Satisfaction Scale.

Results: After reminiscence therapy, Beck Depression Scale and Life Satisfaction Scale mean scores increased in elderly in the intervention group (p<0.05), but there were no significant differences for the UCLA Loneliness Scale mean scores (p>0.05).

Conclusion: At the end of the study, reminiscence therapy was found to be a useful method for reducing depression and increasing life satisfaction in elderly.

Keywords: Memory, aged, nursing homes

Huzurevinde Kalan Yaşlılarda Grup Anımsama Terapisinin Yalnızlık, Depresyon ve Yaşam Doyumuna Etkisi: Randomize Kontrollü Çalışma

ÖZET

Amaç: Bu çalışmada, huzurevinde yaşayan yaşlı bireylerde grup anımsama terapisinin etkisini incelemek amaçlanmıştır.

Yöntem: Bu randomize kontrollü çalışma, Türkiye'de iki huzurevinde gerçekleştirilmiştir. Müdahale grubuna (n= 37) ve kontrol grubuna (n=39) toplam 76 yaşlı katılmıştır. Müdahale grubuna altı hafta boyunca haftada bir kez 30-45 dakika süren grup seansları şeklinde anımsama terapisi uygulandı. Kontrol grubuna ise uygulama yapılmadı. Veriler Sosyodemografik form, Yalnızlık Ölçeği, Beck Depresyon Ölçeği ve Yaşam Doyumu Ölçeği kullanılarak toplanmıştır.

Bulgular: Anımsama terapisinden sonra müdahale grubundaki yaşlılarda Beck Depresyon Ölçeği ve Yaşam Doyumu Ölçeği puan ortalamaları artmıştır (p<0.05). Ancak UCLA Yalnızlık Ölçeği puan ortalamaları arasında anlamlı bir fark bulunmamıştır. (p>0.05).

Sonuç: Araştırmanın sonunda anımsama terapisinin yaşlılarda depresyonu azaltmak ve yaşam doyumunu artırmak için yararlı bir yöntem olduğu bulunmuştur.

Anahtar kelimeler: Hafıza, yaşlı, huzur evleri

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Emotional problems such as loneliness, depression, anxiety may be more prevalent for older people living nursing homes as a result of a range of factors including moving to an unfamiliar environment, deterioration of physical health (1) and lack of social contact (2). Pharmacological (such as psychotropic drugs) or non-pharmacological strategies can be used to prevent emotional problems. Psychotropic drugs have many negative effects (such as; insomnia, falls, hyponatremia, depression, fracture, and epilepsy) (3). Therefore, the use of non-pharmacological treatments such as health education, counseling and psychotherapies can be considered for older adult care (4).

Reminiscence therapy is a non-pharmacological method that can be used to reduce emotional problems (such as anxiety, depression and loneliness) in older adults. Reminiscence is defined as a retrospective process involving important events, past experiences, experiences in the life process of the individual (5). This therapy method is one of the independent roles of nurses in the care of elderly adults (6). This therapy technique first emerged as a practice of nursing and elderly care, then used by professional practitioners such as nursing staff, social workers, psychologists and recreational therapists (7). Since reminiscence therapy is not a medicated treatment method, it is an appropriate psychological approach that is generally used in the elderly (8).

Reminiscence therapy can be made as individual or group therapy. In the reminiscence group, elderly individuals share a significant past event with peers (9). These therapy groups there can be various topics such as forgotten holidays, birthdays, marriage, and first love. Group reminiscence therapy can be performed with groups of 6-10. Groups provide sufficient time for the active participation of each of the elderly and promote group interaction. For therapy to be effective, it is recommended that 6-12 sessions be held and each session lasts 30-90 minutes (6).

There are many studies showing that reminiscence therapy has a positive effect on reducing loneliness and depression (10), increasing positive thinking (11), life satisfaction (12), cognitive level (13), and psychological well-being (7).

The psychological and social needs of elderly people living in nursing homes in Turkey are being organized by nurses, psychologists, social service specialists (14). However, when examined, it is observed that psychological services are not provided at satisfactory levels in these institutions (15). The number of research on nursing and other areas of reminiscence therapy is high, but there are very few studies on the subject in our country. The purpose of this study is to examine the effects of group reminiscence therapy on the loneliness, depression and life satisfaction of the older adults in nursing homes.

The following hypotheses (H) were tested in this study:

H_1. Group reminiscence therapy has an effect on decreasing feeling lonely of elderly in nursing home.

H_2. Group reminiscence therapy has an effect on decreasing depression level of elderly in nursing home.

H_3. Group reminiscence therapy has an effect on increasing life satisfaction of elderly in nursing home.

METHODS

Design and Setting
The randomized controlled trial study was carried out as a between February and July 2017 in two nursing homes in Turkey. Power analysis was used to calculate the sample size (G*Power 3.0.10 program). We assumed that α= 0.05 and power= 0.95. The calculated sample size was 44 participants (intervention group=22 elderly, control group=22 elderly). For the probability of losses during the study, 80 elderly was recruited in study.

Randomization
Eighty elderly who met the inclusion criteria were numbered with 1 to 80. Participants were randomized to intervention (40) or the control group (40). A total of 4 participants dropped out of the study (Figure 1).

Study Inclusion Criteria
*   65 years and older

*   No diagnosis of dementia or psychiatric disorders by a doctor

*   Do not do any other activity that may change the cognitive and functional state

*   Standardized Mini-Mental Examination Test (SMMSE) score of 23 and above.

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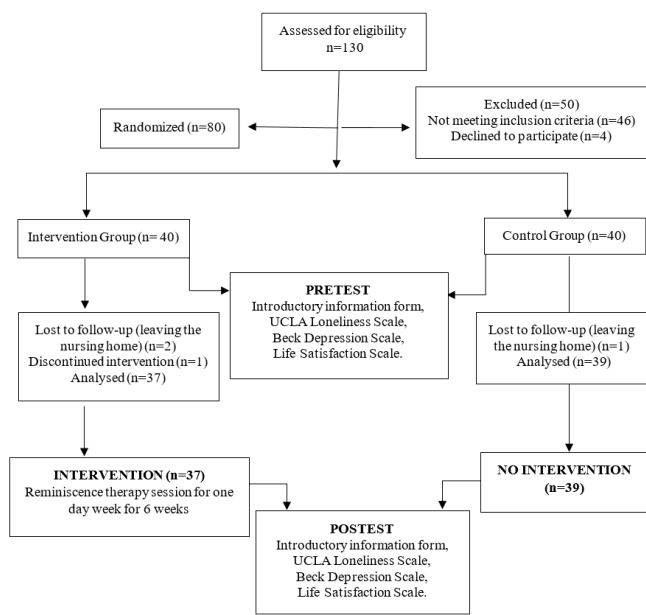
Figure 1. Consort Flow Chart

Measurement

The data of study were collected using an socio-demographic form that was developed by the researcher and evaluated socio-demographic characteristics and disease history of individuals in the intervention and the control groups, SMMSE, UCLA Loneliness Scale (UCLA-LS), Life Satisfaction Scale (LSS), Beck Depression Scale (BDS). Data collection tools were applied to groups during the first interview (pretest) and at the end of 6 weeks (posttest).

SMMSE test was developed by Folstein et al. and Turkish validity and reliability was performed by Güngen, et al (16). It consists of 11 items that evaluate orientation, recording memory, attention and calculation, recall, and language. The total score is calculated out of 30. The limit value is accepted as 23/24 (23 and below points cognitive dysfunction].

UCLA-LS was developed by Russel et al. and Turkish validity and reliability was performed by Demir (1989). Cronbach's alpha reliability coefficient was 0.96. It measured one's subjective feelings of loneliness and feelings of social isolation. The total score is between 20 and 80 points. High scores indicate that individuals are experiencing more loneliness (17).

Life Satisfaction Scale was developed by Neugarten, et al and Karataş (1988) was adapted to Turkish. It estimated how elderly individuals perceive various aspects of life in this direction. The scale consists of 20 questions, with the expressions "yes" and "no". Cronbach's alpha reliability coefficient was 0.94. Seven points and beloved low life satisfaction, 8-12 points mean life satisfaction, 13 points and over are considered high life satisfaction level (18).

BDS was developed by Beck (1961) and Turkish validity and reliability was conducted by Hisli (1988). Cronbach's alpha reliability coefficient was 0.92. It consists of 21 questions, with each question ranging from 0 to 3 points. The score ranges from 1 to 10 normal, mild to moderate from 11 to 16, clinical depression from 17 to 20; moderate depression between 21-30; severe depression between 31 and 40 points; 41-63 are considered as severe depression (19).

Intervention

The intervention group received reminiscence therapy in-group sessions that took 30-45 min, one time every week for six weeks. The control group had no application. Reminiscence therapy sessions consisted of various topics: school or workdays, favorite plants, and animals, childhood and family life, holidays, special celebrations, friendship, neigh boards, evaluation, and closure respectively in the coming weeks. Every week, elderly was asked how they spent the previous week. Then, objects that make it easier to remember the weekly topic were shown them. They shared positive memories. Each session ended with the announcement of the next week's topic.

Ethical Consideration

The Ethics Committee of Marmara University Health Science Institutes Ethics Council granted ethical approval to our study (Approval date/no=09.01.2017/36). Written informed consent was obtained from older adults.

Data Analysis

All statistical analyses were performed on SPSS 22.0. The Kolmogorov Smirnov normality test was applied for the normality test and all scores were found to meet normality assumptions. The independent sample t-test was used to evaluate scales scores differences between groups. The paired sample t-test was used to evaluate scales scores differences pre and posttest. The statistical significance level was accepted as p <0.05.

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RESULTS

In our study, participants 65.7% of them were male, 68.4% were aged between 65-79 years, 90.8 % were single, 48.7% of primary school graduates, 96.1% had at least one chronic disease.

Them of 47.4% stay in a nursing home for over five years. According to the participants' descriptive characteristics, there were no differences between groups. (p>0.05; Table 1).

Them of 47.4% stay in a nursing home for over five years. According to the participants' descriptive characteristics, there were no differences between groups. (p>0.05; Table 1).

Kolmogorov-Smirnov test results showed that confirmed normality distribution UCLA-LS, LSS, BDS scores intervention and control groups (Table 2).

Table 2. Results of normal distribution intervention and control groups on the scales						
	UCLA Loneliness Scale		Life Satisfaction Scale		Beck Depression Scale	
	Z	p	Z	p	Z	p
Intervention	.85	.45	.57	.89	.77	.58
Control	.84	.47	1.15	.13	.88	.41
Z=Kolmogrov Smirnov Z test						

There was no statistically significant difference between the groups' pretest mean scores of all scales (p>0.05) (Table 3).

There was a statistically significant difference between their posttest BDS mean scores of intervention group (p<0.05). The posttest mean score of the intervention group was lower than the pretest. There was no difference pre-posttest UCLA-LS mean score of intervention groups (p>0.05) (Table 3).

There was a statistically significant difference between pre and posttest LSS mean scores of intervention group (p<0.05). The posttest mean score of the intervention group was higher than the pretest. The posttest mean score of the intervention group was higher than the pretest scores. There was no difference pre-posttest UCLA-LS and BDS mean score of control groups (p>0.05) (Table 3).

DISCUSSION

Living in a nursing home may lead to depression, loss of self-efficacy, and loss of trust in personal skills and resources (9). Reminiscence therapy is one type of psychotherapy that could alleviate feelings of loneliness, anxiety and depression among older adults. The focus of group reminiscence therapy is to create meaningful social interactions through sharing memories with other people. There is evidence that this approach helps to encourage meaningful social interaction (20) and a sense of belonging (21). Through the activities of sharing memories in the group, older people experience positive interactions (22) and a sense of social identity may develop (23).

Table 1. Socio-demographic characteristics of participants (n=76)					
Socio-demographic characteristics	Intervention (37)		Control (39)		Statistics
	n	%	n	%	x^2/p
Age					
65-79 age	26	70.3	26	66.7	x^2=.11 p=.73
80 age and over	11	29.7	13	33.3	
Gender					
Male	22	59.5	27	69.2	x^2=.79 p=.37
Female	15	40.5	12	30.8	
Education					
Illiterate	6	16.2	6	15.4	
Primary school graduate	19	51.4	18	46.2	x^2=.30 p=.95
High school graduate	8	21.6	10	25.6	
University graduate	4	10.8	5	12.8	
Having children					
Have children	29	78.4	33	84.6	x^2=.49 p=.48
No children	8	21.6	6	15.4	
Chronic diseases					
Yes	34	91.9	39	100	*x^2=- p=.11
No	3	8.1	0	0	
Length of stay					
1-4 year	19	51.4	21	53.8	x^2=.47 p=.82
5 year and over	18	48.6	18	46.2	
x^2= ki kare test					

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Table 3. Comparison of the intervention and control groups according to their UCLA Loneliness, Life Satisfaction, Beck Depression Scale scores (n=76)									
	UCLA Loneliness		**Test value**	**Life Satisfaction**		**Test value**	**Beck Depression**		**Test value**
	Pretest	**Post test**	**t/p**	**Pretest**	**Posttest**	**t/p**	**Pretest**	**Posttest**	**t/p**
	Mean±SD	**Mean±SD**		**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Intervention	50.67±8.66	48.43±4.81	1.53/.13	18.67±7.03	22.13±5.70	-6.50/.*00	21.43±10.42	18.21±8.76	3.87/.*00
Control	49.84±9.12	47.38±4.53	1.71/.09	19.38±8.40	19.82±7.83	-1.85/.*07	18.94±10.02	19.74±8.38	-1.12/.*26
Test value	**t=.40/.68.	**t=.97/.33		**t= .39/.79	**t=.61/.53		**t=1.05/.29	**t=..77/.44	
*t= paired sample t test, **t= independent sample t test									

This randomized controlled study assessed the effect of group reminiscence therapy on the loneliness, life satisfaction and depression of the elderly living in a nursing home. The study results confirm the hypothesis that "reminiscence therapy increasing the life satisfaction of the elderly in the nursing home". Ching Teng, et al (24) found that group reminiscence therapy improves the life satisfaction of the elders. Refahi and Ghaforiyan (25) find that group reminiscence therapy had a positive influence on the self-esteem and life satisfaction of the elderly. The study results confirm the hypothesis that "group reminiscence therapy decreasing depression level of elderly in the nursing home." This finding is consistent with other research results (9,22,24,25).

The study results do not confirm the hypothesis that " group reminiscence therapy reduces the sense of loneliness of seniors in the nursing home ". The results of the quasi-experimental design study which was performed by Nooripour, et al (26) in reminiscence intervention (12 sessions) indicated that reminiscence decreased loneliness feeling. Sahu, et al (27) find that reminiscence therapy decreasing loneliness of the elderly. These results were due to different our study methodological approaches such as different research groups, number of sessions. Additionally, Syead Elias, et al (28) stated that needs more evidence of the effect of reminiscence therapy on reducing the loneliness of older adults.

Reminiscence therapy is useful to overcome depression among elderly. The nurse can know the personality of each elderly so as to improve the quality of nursing care for elderly (29). The results confirm the hypothesis that "group reminiscence therapy has an effect on decreasing depression level of elderly in nursing home." This finding is consistent with the findings of pre-existing research and systematic rewiev studies on the efficacy of reminiscence

therapies on the rate of depression in the elderly people (22,24,29,30).

LIMITATIONS

This study had several limitations. Firstly, the study was conducted with just two nursing homes. Secondly, there was no follow-up in the study. Thirdly, the duration of the study was a short period of six weeks. Long-term studies can be conducted in different institutions to test the effectiveness of this group therapy program.

CONCLUSION

According to research reminiscence therapy increased to life satisfaction and decrease depression of the elderly living in nursing homes. Reminiscence therapy can be used as a nursing intervention.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nutrition and Dietetics / Beslenme ve Diyetetik

Assessment of the Relationship between University Students' Food Consumption and Anthropometric Measurements and Phase Angle

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ABSTRACT

Purpose: This study was carried out to assess the relationship between university students' food consumption and anthropometric measurements, and phase angle (PA).

Methods: The study was conducted with a total of 240 students between the ages of 18-25 studying at the Department of Nutrition and Dietetics at Agri Ibrahim Cecen University Health School. Research data were collected using a questionnaire that included about demographic information and questions about physical activity levels and three-day food consumption record was taken. Lastly, anthropometric measurements of the students were performed by the researcher in person.

Results: The study's findings revealed that the students' energy intake was lower than their energy expenditures. The body mass indexes (BMI), and waist circumferences of female and male students were calculated as 21.8 ± 3.2 kg/m^2 and 23 ± 3.4 kg/m^2, and 75.2 ± 8.1 cm and 85 ± 10 cm, respectively. The PA was $5.7 \pm 0.5°$ in female students and $6.7 \pm 0.5°$ in male students ($p<0.05$).

Conclusion: The study's findings revealed that male students had significantly higher PA values. The PA values of female students were found to have increased with BMI, waist circumference, and body muscle mass values. There was also no significant relationship between students' PA values and and food consumption levels regardless of gender.

Keywords: Bioelectrical impedance, body mass index, food intake

Üniversite Öğrencilerinin Besin Tüketimleri ve Antropometrik Ölçümleri ile Faz Açısı Arasındaki İlişkinin Değerlendirilmesi

ÖZET

Amaç: Araştırma, üniversite öğrencilerinin besin tüketimleri ve antropometrik ölçümleri ile faz açısı arasındaki ilişkinin değerlendirilmesi amacı ile yapılmıştır.

Yöntem: Çalışma Ağrı İbrahim Çeçen Üniversitesi Sağlık Yüksekokulu Beslenme ve Diyetetik bölümünde öğrenim gören 18-25 yaş aralığındaki toplam 240 öğrenci ile yapılmıştır. Çalışmaya katılan öğrencilerin demografik bilgileri, fiziksel aktivite kayıt düzeyleri sorgulanarak üç günlük besin tüketim kaydı alınmıştır. Katılımcıların antropometrik ölçümleri araştırmacı tarafından birebir ölçülerek alınmıştır.

Bulgular: Öğrencilerin enerji alımlarının enerji harcamasından düşük olduğu bulunmuştur. Beden kütle indeksi (BKİ) kız öğrencilerde $21,8 \pm 3,2$ kg/m^2 erkek öğrencilerde $23 \pm 3,4$ kg/m^2, bel çevresi kız öğrencilerde $75,2 \pm 8,1$ cm erkek öğrencilerde 85 ± 10 cm'dir. Faz açısı erkek öğrencilerde $6,7 \pm 0,5°$ kız öğrencilerde $5,7 \pm 0,5°$ olduğu saptanmıştır ($p<0,05$).

Sonuç: Çalışmaya katılan erkek öğrencilerin daha yüksek faz açısı değerine sahip olduğu görülmüştür. Kız öğrencilerin PA değerlerinin BKİ, bel çevresi ve vücut kas kütlesi değerleri ile arttığı bulunmuştur. Öğrencilerin besin tüketimleri ile faz açısı arasında bir ilişki bulunmamıştır.

Anahtar kelimeler: Beden kütle indeksi, besin alımı, biyoelektrik empedans

Contributions of dietary fat, carbohydrate, and protein to energy intake were reported to be associated with body weight and obesity prevalence (1). Diets low in fibers and high in fats have been associated with the most significant increases in the risk of becoming overweight and obese (2,3).

Anthropometric measurements are essential in determining the nutritional levels of individuals as they are indicators of the proteins and fats stored in the body (4). Bioelectrical impedance analysis (BIA) evaluates body composition by the correlation between body water content and impedance (5).

BIA measures the whole-body impedance along with the two components of impedance, that is, reactance (Xc) and resistance (R) (6). The PA, the direct index of the BIA device, is derived from the relationship between the Xc and R measurements in order to obtain more valid assessments that directly reflect tissue hydration and integrity. The PA is calculated by the formula (arctan (Xc/R) $\times$(180/π) (7).

The PA is considered an indicator of body cell mass and nutritional level (8). Low PA values indicate cell death or decreased cell membrane integrity and decreased cell function. In contrast, high PA values indicate better cell membrane integrity, cell function, and body cell mass. PA values vary between 5° and 7° in healthy individuals (9).

In the light of the above considerations, this study was carried out to assess the relationship between university students' food consumption and anthropometric measurements, and PA.

MATERIAL and METHODS

Study Group and Design
The study group of this study comprised a total of 240 students aged between 18-25, who were studying at the Department of Nutrition and Dietetics at Agri Ibrahim Cecen University School of Health and volunteered to participate in the study. Research data were collected using a questionnaire that included questions about demographic information, physical activity levels and three-day food consumption records were taken. Lastly, anthropometric measurements of the students were performed by the researcher in person.

Assessment of Physical Activity Levels
The physical activity levels of the study students were evaluated through a one-day physical activity record form. To this end, first, the physical activities were classified according to their categories, and secondly, the duration of the physical activities was multiplied by the energy cost coefficient. The products have been added and then divided by 24 hours to determine the physical activity level (Pal) for each study participant (10).

Assessment of Food Consumption
Students' daily energy and nutrient intake were evaluated based on their three-day food consumption record. Serving size training was provided to the study students based on the 'Food and Food Photo Catalogue' (11).

Assessment of Anthropometric Measurements
Students' waist circumferences were measured from the midpoint between the lowest rib and the lateral iliac crest while standing using a rigid tape measure (12). Students' heights were measured while standing on the Frankfort horizontal plane using a commercial stadiometer, a Tartı brand telescopic height gauge. Students' body weights were measured on bare feet and while they had light clothing on using a Tanita MC 780 brand BIA device. Additionally, students body fat percentage (%), body fat mass (kg), body muscle mass (kg), and PA were determined according to age and gender using BIA.

The students' body mass indexes (BMI) were assessed according to the BMI criteria published by the World Health Organization (13). Basal metabolic rates (BMR) of the students included in the study were calculated using the Harris-Benedict equation based on whether they were classified as underweight, normal, or slightly overweight according to the BMI criteria (14). In addition, BMRs of the students who were classified as obese according to the BMI criteria were calculated using the Mifflin-St Jeor equation (15). Total energy requirements of the students were found by multiplying their BMR and physical activity level (Pal) values (14). The PA value commonly varies between 5° and 7° in healthy students (9).

Statistical Analysis
SPSS (IBM Statistical Package for Social Sciences for Windows, version 23.0, Chicago, IL, USA) software package was used to analyze the research data. Descriptive statistics were expressed as numbers (n) and percentages (%), mean ($\dot{X}$) ± standard deviation (SD), median, maximum and minimum values. Independent samples t-test was used to research data determined to conform to normal distribution. The Mann-Whitney U test was used to of non-parametric research data. Pearson's and Spearman's

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correlation tests were used to assess the linear relationship between variables in the case of the normally and non-normally distributed research data, respectively. $p<0.05$ was considered statistically significant.

RESULTS

A total of 240 university students, of whom 195 were female and 45 were male, participated in the study. The mean ages of male students 21.7 ± 1.6 years female were calculated as 20.8 ± 1.3 years. It was determined that 60.5% and 39.5% of the female students have been taking day and night classes, respectively, as compared to 55.6% and 44.4% of the male students who were determined to have been taking day and night classes, respectively. In addition, 90.3% of the female students and 73.3% of the male students were determined to have been living in dormitories (Table 1).

Based on the three-day food consumption records of the students, it was determined that mean daily energy intake through diet, mean intake of carbohydrate, protein, fat, saturated fatty acid, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, cholesterol, fiber, water-soluble fiber, and water-insoluble fiber were significantly higher in male students than in female students ($p<0.05$). Additionally, the percentage of energy coming from fats was found to be significantly higher in female students than in male students ($p<0.05$) (Table 2).

The mean body weight, height, BMI, waist circumference, body muscle mass, BMR, Pal values, and total energy expenditures of male students were found to be significantly higher than female students ($p<0.05$). On the other hand, the mean body fat mass and body fat percentage of female students were found to be significantly higher than male students ($p<0,05$). Male and female students' mean PA values were found as 6.7 ± 0.5º and 5.7 ± 0.5º, respectively, and significantly differed between the genders ($p<0.05$) (Table 3).

As for the relationship between PA and anthropometric measurements, statistically significant and positive relationships were found between PA and the anthropometric measurements, i.e., body muscle mass, waist circumference, and BMI values (r=0.264, $p<0.001$; r=0.186, $p=0.009$; and r=0.323, $p<0,001$; respectively) in female students, whereas no significant relationship was found between PA and any anthropometric measurement in male students ($p>0,05$). In addition, male and female students no significant relationship was found between the PA values

and mean daily energy, carbohydrate, protein, and fat intake through diet ($p>0,05$) (Table 4).

DISCUSSION

Adults should get 45-60% of their daily energy from carbohydrates, 20-35% from fats, and 10-20% from proteins (16). In comparison, in this study, it was determined that students' energy intake ratios from carbohydrates, fats, and proteins were within the recommended value range indicated above; however, that their energy intakes were lower than their energy expenditures (Table 2).

It was reported in the studies conducted with university students that the mean body weight, BMI, and body muscle mass values of male students were significantly higher than female students, whereas that the mean body fat percentage and body fat mass values of female students were significantly higher than male students (17–19). Similarly, in this study, the mean body weight, BMI, and body muscle mass values of male students were found to be significantly higher than female students, and the mean body fat percentage and body fat mass values of female students were found to be significantly higher than male students. Additionally, in this study, it was determined that 17.8% and 13.8% of the male and female students were overweight, respectively, and that 4.4% and 2.1% of the male and female students were obese, respectively (Table 3).

In healthy individuals, the PA value commonly varies between 5° and 7°. Low PA values indicate cell death or decreased cell membrane integrity and cell function. In contrast, high PA values indicate better cell membrane integrity and cell function, and body cell mass (9,20). The results of the studies available in the literature indicate that PA values below the range of 4.4° to 5.4° are associated with malnutrition and low survival rates (20,21). In a study conducted with 75 female students between the ages of 20-65 in Turkey, the mean PA of the students was found as 5.9±0.8º (22). In comparison, in this study, the mean PA values of the male and female students were found as 6.7 ± 0.5º and 5.7 ± 0.5º, respectively (Table 3). Accordingly, it was determined that the PA values, the indicator of the health status featuring cell health and cell membrane integrity, were within the normal range in male and female students.

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Table 1. Demographic characteristics of the study students			
		Gender	
	Overall (n=240)	**Female (n=195)**	**Male (n=45)**
Age Ẋ ± SD	21 ± 1.4	20.8 ± 1.3	21.7 ± 1.6
Education type, n (%)			
Formal education	143 (59.6)	118 (60.5)	25 (55.6)
Secondary education	97 (40.4)	77 (39.5)	20 (44.4)
Housing status, n (%)			
I live in a state dormitory	209 (87.1)	176 (90.3)	33 (73.3)
I live with my family	13 (5.4)	11 (5.6)	2 (4.4)
I'm staying in a rented house with my friends	18 (7.5)	8 (4.1)	10 (22.2)
Working status, n (%)			
I'm working	11 (4.6)	9 (4.6)	2 (4.4)
I am not working	229 (95.4)	186 (95.4)	43 (95.6)
Smoking status, n (%)			
Yes	37 (15.4)	16 (8.2)	21 (46.7)
No	193 (80.4)	175 (89.7)	18 (40)
I do not use it anymore	10 (4.2)	4 (2.1)	6 (13.3)
Alcohol drinking status, n (%)			
Yes	7 (2.9)	2 (1)	5 (11.1)
No	224 (93.3)	188 (96.4)	36 (80)
Sometimes	9 (3.8)	5 (2.6)	4 (8.9)

Table 2. Students' mean energy and macronutrients intake through diet					
	Female (n=195)		**Male (n=45)**		**p**
	Ẋ ± SD	**Median (Min-Max)**	**Ẋ ± SD**	**Median (Min-Max)**	
Energy (kcal)	1339.5 ± 356.5	1296.4 (517.2 – 2835.7)	1747.4 ± 393.5	1742.4 (737.1 – 2767.6)	**<0.001**
Carbohydrate (g)	160.2 ± 49.1	156.9 (55.4 – 336.5)	211.0 ± 50.2	214.1 (106.3 – 354.5)	**<0.001**
Carbohydrate %	48.8 ± 6.4	49 (24 – 73)	49.4 ± 4.5	49 (40 – 62)	0.446
Protein (g)	53.6 ± 14.1	52.7 (15.6 – 106.1)	73.8 ± 17.6	73.6 (31.9 – 113.4)	**<0.001**
Protein %	16.5 ± 2.3	17 (9 – 24)	17.3 ± 2.5	17 (12 – 26)	0.061
Fat (g)	51.9 ± 16.4	50.2 (8.1 – 136)	65.4 ± 18.2	61.8 (19.2 – 120)	**<0.001**
Fat %	34.5 ± 5.6	35 (14 – 55)	33.1 ± 4.1	33 (23 – 42)	**0.049**
SFA (g)	21.0 ± 6.7	20.8 (3.7 – 49.6)	25.0 ± 6.4	25.2 (6.7 – 42.1)	**<0.001**
MUFA (g)	17.1 ± 5.4	16.6 (2.9 – 37.8)	21.5 ± 6.9	20.7 (5.9 – 44.9)	**<0.001**
PUFA (g)	9.5 ± 4.7	8.3 (1.7 – 39)	13.1 ± 5.8	11.9 (4.5 – 33.7)	**<0.001**
Omega 3 (g)	1.1 ± 0.7	0.9 (0.4 – 6.4)	1.4 ± 0.7	1.2 (0.5 – 4.1)	**<0.001**
Omega 6 (g)	7.9 ± 4.0	7.1 (1.2 – 32.4)	11.0 ± 5.2	9.8 (3.7 – 30.6)	**<0.001**
Cholesterol (mg)	255.3 ± 120.9	239.5 (15.3 – 760.1)	326.2 ± 115.3	319.1 (127.8 – 572.8)	**<0.001**
Fiber (g)	14.9 ± 4.9	14.2 (4.3 – 31)	17.4 ± 5.4	16.7 (8.7 – 31.2)	**0.004**
Water soluble fiber (g)	4.9 ± 1.7	4.6 (1.6 – 13)	5.8 ± 1.8	5.7 (2.7 – 12.4)	**0.003**
Water insoluble fiber (g)	9.0 ± 3.1	8.6 (2.8 – 22)	10.9 ± 3.8	10.6 (5.3 – 20.5)	**0.002**
SFA: Saturated fatty acids MUFA: Monounsaturated fatty acids PUFA : polyunsaturated fatty acids					

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Table 3. Students' anthropometric measurements, physical activity levels and energy expenditures					
	Female (n=195)		**Male (n=45)**		**p**
	Ẋ ± SD	**Median (Min-Max)**	**Ẋ ± SD**	**Median (Min-Max)**	
Body weight (kg)	57.2 ± 9.8	55.2 (38.1 – 94.8)	71.7 ± 11.8	69.6 (49.2 – 104.1)	**<0.001**
Height (cm)	161.7 ± 5.3	162 (149 – 173)	176.3 ± 5.5	175 (166 – 190)	**<0.001**
BMI (kg/m^2)	21.8 ± 3.2	21.2 (14.9 – 33.6)	23 ± 3.4	23.2 (16.4 – 32.1)	**0.013**
Waist circumference (cm)	75.2 ± 8.1	74 (60 – 102)	85 ± 10	84 (69 – 112)	**<0.001**
Body muscle (kg)	41 ± 4.5	40.2 (30.4 – 58.9)	57.2 ± 5.9	56.9 (45.1 – 74.6)	**<0.001**
Body fat (%)	23.7 ± 6.1	23.1 (11.1 – 43.6)	15.1 ± 6.7	15.6 (3.5 – 28.8)	**<0.001**
Body fat (kg)	14.1 ± 6.1	12.8 (5 – 39.4)	11.5 ± 6.7	11.2 (1.7 – 30)	**0.004**
Phase angle °	5.7 ± 0.5	5.6 (4.1 – 8.9)	6.7 ± 0.5	6.7 (5.8 – 7.8)	**<0.001**
BMI (kcal)	1409.4 ± 118.5	1385.6 (1217.2 – 1739.2)	1779.1 ± 159.1	1763.5 (1475.7 – 2200)	**0.001**
Pal	1.6 ± 0.2	1.6 (1.3 – 2.7)	1.7 ± 0.2	1.7 (1.3 – 2.4)	**0.006**
Energy expenditure (kcal)	2302.6 ± 255.2	2286.7 (1809.6 – 3586.7)	3075.7 ± 441.6	3084.8 (2173.5 – 4383.4)	**<0.001**
BMI: body mass index					

Table 4. The relationship between students' phase angle values and daily energy and macronutrient intakes, and anthropometric measurements				
	Phase Angle °			
	Female		**Male**	
	r	**p**	**r**	**p**
BMI (kg/m^2)	0.323	**<0.001**	0.234	0.122
Waist circumference (cm)	0.186	**0.009**	0.016	0.918
Body muscle (kg)	0.264	**<0.001**	0.041	0.79
Body fat (%)	0.01	0.887	0.104	0.497
Body fat (kg)	0.077	0.287	0.107	0.483
Pal	0.038	0.595	-0.141	0.356
Energy (kcal)	-0.052	0.467	-0.038	0.804
Carbohydrate (g)	-0.073	0.309	-0.048	0.756
Carbohydrate (%)	-0.045	0.534	-0.185	0.224
Protein (g)	0.021	0.774	0.148	0.333
Protein (%)	0.059	0.412	0.132	0.387
Fat (g)	-0.019	0.792	-0.027	0.858
Fat (%)	0.027	0.709	-0.051	0.739
BMI: body mass index				

In healthy individuals, gender, age, lean body mass, BMI, and body fluid distribution are considered as essential determinants of PA (5,23,24). Since males have more body muscle mass relative to their body weight as compared to females, they also have higher PA values than females due to the decrease in resistance (25). In parallel, in this study, the mean body muscle mass, thus the mean PA value of ale students were found to be significantly higher than female students (p<0.05) (Table 3).

The results of the studies conducted on PA indicated a negative correlation between the PA and body fat ratio and a positive correlation between the PA and the body muscle mass. Furthermore, the results of the relevant studies available in the literature have revealed that the PA values increase with increasing BMI values due to the increased number of muscle and fat cells (5,23). In comparison, in this study, there was a statistically significant and positive relationship between the PA and body muscle mass, waist circumference, and BMI values in female students; however, there was no statistically significant relationship between the PA and anthropometric measurements in male students (Table 4).

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The absence of a significant relationship between the PA and anthropometric measurements in male students in this study was attributed to the fact that the sample size of the male students, which was smaller compared to the sample size of female students, might not have been enough to reveal the effect of anthropometric measurements on the PA.

A study conducted with female students in Turkey reported a significantly positive relationship between the PA and the BMI and body muscle mass values. However, in the same study, no statistically significant relationship was found between the PA and the physical activity levels and macronutrient intake (22). In comparison, in this study, no significant relationship was found between the PA and the daily energy and macronutrient intake through diet and Pal values (Table 4).

CONCLUSION

The results of this study indicated that the students who participated in the study energy intake was lower than their energy expenditure. Additionally, it was observed that the PA values of the female and male students participating in the study were within the normal range and were found to have significantly differed between genders in favor of male students. The PA of female students were found to have increased with BMI, waist circumference, and body muscle mass values. In contrast, there was no significant relationship between the PA values and anthropometric measurements in male students. There was also no significant relationship between students' PA values and the physical activity and food consumption levels regardless of gender. Taking into consideration that PA is used as one of the anthropometric indicators to determine the body cell mass and nutritional status, it should be further investigated in larger populations of different age groups in Turkish society.

DECLARATIONS

Ethics Approval

The study's research design was approved by the Acibadem Mehmet Ali Aydinlar University Medical Research Evaluation Committee with the ethics committee approval numbered 2020-02/42. In addition, written permission of the Directorate of Agri Ibrahim Cecen University School of Health, as the venue where the study is to be conducted, was obtained. Lastly, the written consent of all students who participated in the study was obtained after they were orally informed about the study.

Authors' Contributions
Concept: ME, GAÇ; Study Design: ME, GAÇ; Data Collection: ME; Data Analysis: ME, GAÇ; Literature Search: ME; Writing Manuscript: ME; Critical Review: GAÇ

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nutrition and Dietetics / Beslenme ve Diyetetik

The Relationship Between Nutrition Literacy and Diet Self-Efficacy in Individuals who Have Cardiovascular Disease or Cardiovascular Risk Factors Receiving Dietary Therapy

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ABSTRACT

Purpose: We aimed to determine the nutrition literacy and diet self-efficacy levels of individuals who have a cardiovascular disease or risk factors and receive medical nutrition therapy, and to determine the effect of nutrition literacy on diet self-efficacy.

Methods: A total number of 150 participants were included in the study between November 2019 and February 2020. Their height, body weight, and waist circumference were measured, age, gender, educational levels, place of residence were questioned, and "Nutrition Literacy Assessment Tool in Adults" and "Self-Efficacy Scale in the Regulation Nutritional Habits in Cardiac Patients" were used for data collection.

Results: A significant difference was found between the educational levels of the participants, their place of residence, and their nutrition literacy levels (p<0.05). The nutrition literacy levels of all participants were determined to be "borderline". All individuals participating in the study were found to have low diet self-efficacy levels. A very significant positive correlation was found between diet self-efficacy levels and nutrition literacy levels and components of nutrition literacy among the individuals participating in the study (p<0.05).

Conclusion: Dietary therapy and nutrition education plays an important role in individuals with cardiovascular disease and risk factors. Nutrition education for these individuals may be beneficial by also considering their nutrition literacy and diet self-efficacy levels.

Keywords: Nutrition Literacy; Self-Efficacy; Cardiovascular Disease

Kardiyovasküler Hastalık veya Kardiyovasküler Risk Faktörlerine Sahip ve Tıbbi Beslenme Tedavisi Alan Bireylerde Beslenme Okuryazarlığı ve Diyet Öz Yeterliliği

ÖZET

Amaç: Bu çalışmada kardiyovasküler hastalığa veya risk faktörlerine sahip olup, tıbbi beslenme tedavisi alan bireylerde beslenme okuryazarlığı ve diyet öz yeterliliğinin saptnması, beslenme okuryazarlığının diyet öz yeterliliğine etkisinin değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmaya Kasım 2019 – Şubat 2020 tarihleri arasında 150 birey dahil edilmiş, boy uzunluğu, vücut ağırlığı ve bel çevreleri ölçümleri yapılmış, veri toplamak için sorgulanan yaş, cinsiyet, eğitim durumu, yaşanılan bölge gibi sosyodemografik özelliklerine ek olarak Yetişkinlerde Beslenme Okuryazarlığı Değerlendirme Aracı ve kalp hastalarında beslenme alışkanlıklarının düzenlenmesinde Öz Yeterlilik Ölçeği kullanılmıştır.

Bulgular: Bireylerin eğitim seviyesi ve yaşadıkları bölge ile beslenme okuryazarlığı arasında anlamlı bir ilişki olduğu (p<0.05), tüm katılımcıların beslenme okuryazarlığının sınırda olduğu saptanmıştır. Diyet öz yeterliliğinin tüm katılımcılarda düşük olduğu bulunmuştur. Diyet öz yeterliliği ile beslenme okuryazarlık seviyesi ve beslenme okuryazalığı bileşenleri anlamlı derecede pozitif korelasyon göstermiştir (p<0.05).

Sonuç: Tıbbi beslenme tedavisi ve beslenme eğitimi kardiyovasküler hastalığa veya risk faktörlerine sahip olan bireyler için önemli bir rol oynamaktadır. Bu bireyler için beslenme eğitiminin beslenme okuryazarlığı ve diyet öz yeterliliğinin de kapsayacak şekilde planlanmasının faydalı olacağı düşünülmektedir.

Anahtar Kelimeler: Beslenme Okuryazarlığı, Öz Yeterlilik, Kardiyovasküler Hastalıklar

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Cardiovascular disease (CVD) and risk factors are health problems that can be prevented by a healthy diet and lifestyle modifications, or that can be treated with medical therapy, medical nutritional therapy, and lifestyle modifications (1). One of the most effective factors for successful nutritional therapy is nutrition literacy, thus successful nutritional therapy is related to nutrition literacy level (2). Nutrition education plays an important role in both the prevention and treatment of increasing chronic diseases (especially cardiovascular diseases and their risk factors). However, nutritional knowledge is complex and may require high levels of cognitive skills (2,3). Self-efficacy is a considerable factor for both medical nutrition therapy and lifestyle changes, and diet self-efficacy is a factor that shows individuals' trust that they will adhere to their nutrition programs (4). Although nutrition has a critical preventive and therapeutic role in CVDs, which have been the primary cause of death worldwide for years, the number of studies on nutrition literacy and dietary self-efficacy is limited (5).

We aimed to determine the nutrition literacy and dietary self-efficacy levels of individuals who have a cardiovascular disease or risk factors and receive medical nutrition therapy (MNT), and to determine the effect of nutrition literacy on dietary self-efficacy levels, thus promoting the development of effective nutrition interventions for individuals with CVD and risk factors.

MATERIALS AND METHODS

Participants

The sample size of the study was calculated as 138 with a 95% confidence interval, by predicting a 0.3-level correlation between the "Nutrition Literacy Assessment Tool in Adults (NLATA) and the Self-Efficacy Scale". Between November 2019 and February 2020 all individuals who applied to the diet policlinic of a public city hospital and complied with the inclusion criteria were included in the study. Inclusion criteria were being a volunteer; diagnosed with cardiovascular disease or cardiovascular risk factors including hypertension, hyperlipidemia, dyslipidemia, hypercholesterolemia, and receiving medical nutrition therapy; being between 18-65 years of age, and being literate. Thus, we included 150 participants who met the inclusion criteria and approved the written informed consent form.

Data Collection

This study included two scales: "Nutrition Literacy Assessment Tool in Adults" and "The Self-Efficacy Scale in the Regulation of Nutritional Habits in Heart Patients"; additionally, a data collection form in which sociodemographic characteristics and anthropometric measurements were documented.

Nutrition Literacy Assessment Tool in Adults evaluating the health and nutrition literacy assessment tools was developed by Cesur, in 2015. It has consisted of 5 parts: (a) general nutrition information section; (b) reading comprehension section; (c) food groups section; (d) portion quantities section; (e) numeracy literacy and food label reading section. The total score is determined by summing the scores from the sub-sections. The highest score that can be obtained is 35. The evaluation of the total score is as follows: 0-11 points are defined as insufficient; 12-23 points borderline; 24-35 points based on sufficient nutrition literacy level (6).

The Turkish validity reliability of the "Self-Efficacy Scale in the Regulation of Nutritional Habits in Cardiac Patients" developed by Bandura (7) was made by Argon and Sevinç in 2010 (8). The Self-Efficacy Scale in the Regulation of Nutritional Habits in Cardiac Patients determines the self-rating of the participants for their performance in the regular nutritional routine. The participants determine the scoring from 0 (not possible) to 50 (can be done at the intermediate level) and 100 (can be done precisely) at intervals of 10 units, depending on the strength of their efficacy beliefs. As the total score obtained from the scale increases, the self-efficacy of the individual is high, and the lower the self-efficacy as it decreases (8).

Anthropometric measurements of the participants were taken by the researcher. Body weight measurement of the participants was measured with a weight-sensitive scale (Health O Meter Professional – 599 KL) of 0.1 kg taking care to dress as thinly as possible. The height of the participants was measured with a stadiometer while the individual was in an upright position, while Frankfort was standing in the plane (the ear canal and the lower border of the orbital-eye socket, the gaze was parallel to the ground), with a sensitivity of 0.1 cm. Measurement of waist circumference of the participants was made by measuring the perimeter between the lower rib and iliac bone with the inelastic tape measure based on the recommendation of the World Health Organization (2000). Body mass index (BMI) was calculated by dividing body weight by square meter of height [body weight (kg)/height (m)]. The participants were classified as underweight, normal body weight, overweight, class I obesity, class II obesity, and class III obesity according to their BMI values as: below 18.5 kg/m² between 18.5-24.9 kg/m² 25.0-29.90 kg/m2 30.0-34.9

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kg/m² 35.0-39.9 kg/m² and above 40 kg/m² respectively. The waist circumference of the participants was classified as <88 cm or ≥ 88 cm for women and <102 cm or ≥ 102 cm for men regarding the disease risk (9).

Statistical Analysis

Statistical evaluation was performed with IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. After The appropriateness of the measurable data to normal distribution was examined by the Shapiro Wilk test, for those with normal distribution, t-test and variance analysis were used in the independent group, Mann Whitney U test and Kruskal Wallis variance analysis were used to evaluate data that did not conform to the normal distribution. The Pearson or Spearman correlation analysis for appropriate was used to examine the relationships between the variables. One of the chi-square tests suitable for qualitative data was used. Median (min-max) values and arithmetic mean ± standard deviation and numbers and percentages were given as descriptive statistics. For all statistics, p-value <0.05 was accepted as significant.

RESULTS

The total number of women participants was 109 (72.66 %) and 41 of the participants were men. The mean age of women and men participants was 52.56±8.86 and 56.00±6.55 years, respectively. The mean BMI of women and men was 36.93±6.23 kg/m² and 33.39±5.21 kg/m², respectively and 37.30 % of total participants were class I. obese and 28.70 % were class II. obese.

The total score of the Nutrition Literacy Assessment Tool in Adults (NLATA) was 20.31±7.62 (borderline) and 20.56±7.41 (borderline) among women and men, respectively. Nutrition Literacy Assessment Tool (NLATA) classification and its relationship with educational status, age, place of residence, and medical nutrition therapy interview frequency by gender are given in Table 1.

Table 1. Nutrition Literacy Assessment Tool (NLATA) Classification and Its Relationship with Educational Status, Age, Place of Residence and Medical Nutrition Therapy Interview Frequency by Gender

	NLATA TOTAL SCORE CLASSIFICATION											
	Women (n=109)						Men (n=41)					
	Insufficient		Borderline		Sufficient		x^2 p	Insufficient		Borderline		Sufficient		x^2 p
	n	%	n	%	n	%		n	%	n	%	n	%	
Educational Status													
Primary school	11	19.30	39	68.40	7	12.30	x^2=42.769 p=0.000*	4	23.50	11	64.70	2	11.80	x^2=14.596 p=0.024*
Secondary school	3	23.10	6	46.20	4	30.80		1	14.30	4	57.10	2	28.60	
High school	1	4.30	4	17.40	18	78.30		1	8.30	5	41.70	6	50.00	
Undergraduate and above	0	0.00	4	25.00	12	75.00		0	0.00	0	0.00	5	100.00	
Age (year)													
18-24	0	0.00	1	50.00	1	50.0	x^2=18.314 p=0.019*	0	0.00	0	0.00	0	0.00	x^2=3.865 p=0.425
25-30	0	0.00	0	0.00	2	100.0		0	0.00	0	0.00	0	0.00	
31-37	0	0.00	0	0.00	3	100.0		0	0.00	1	100.00	0	0.00	
38-50	1	3.80	10	38.50	15	57.70		1	12.50	2	25.00	5	62.50	
51-64	14	18.40	42	55.30	20	26.30		5	15.60	17	53.10	10	31.30	
Place of Residence													
City	10	12.50	30	37.50	40	50.00	x^2=20.262 p=0.000*	4	17.40	6	26.10	13	56.50	x^2=11.495 p=0.003*
Rural	5	17.20	23	79.30	1	3.40		2	11.10	14	77.80	2	11.10	
Medical Nutrition Therapy Interview Frequency													
No	8	23.50	20	58.80	6	17.60	x^2=12.112 p=0.017*	4	23.50	7	41.20	6	35.30	x^2=2.282 p=0.684
1 time	4	10.30	20	51.30	15	38.50		2	10.50	10	52.60	7	36.80	
>1 time	3	8.30	13	36.10	20	55.60		0	0.00	3	60.00	2	40.00	
0-11 points: insufficient literacy level, 12-23 points: borderline literacy level, 24-35 points: sufficient literacy level. In-group analysis: chi-square test analysis. p * <0.05													

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When the NLATA total score classification of the participants are evaluated by gender, a significant difference was found between the educational status, age, place of residence, and medical nutrition therapy interview frequency in women, and the educational status and place of residence in men and NLATA total scores ($p<0.05$).

Regarding the nutrition literacy levels of women, age; body weight; BMI, and waist circumference were evaluated and only a significant difference was found in age ($p<0.001$) while there was no significant difference for men ($p>0.05$).

There was a significant negative correlation between the general nutritional knowledge, reading comprehension, numeracy literacy and food label reading sections score and nutrition literacy total scores, and age among women ($p<0.01$). A significant positive correlation was found between the educational status and the scores obtained from all sections of NLATA and their total scores ($p<0.001$). Between place of residence and all other department scores and total scores, except NLATA food groups and portion quantities, there was a significant negative correlation ($p<0.001$).

Between the place of residence and portion quantities section scores, a significant negative correlation was found ($p< 0.05$).

NLATA scores of men showed that there was a significant positive correlation between general nutritional information, reading comprehension, numeracy literacy, food label reading sections scores and total scores, and educational status ($p<0.01$). A significant negative correlation ($p< 0.05$) was found between the place of residence and all the scores of the sections except for the NLATA food groups section, and a significant negative correlation was found between the place of residence and the total score ($p<0.01$). A significant negative correlation was found between the food groups section scores and waist circumference and BMI values ($p=0.006$ and $p=0.003$, respectively, $p<0.01$).

The mean total scores of participants on the diet self-efficacy scale were 1434.87 ± 736.72. The classification of the total scores of the Diet Self-Efficacy Scale (DSES) of the participants and its relationship with educational status, age, place of residence, and medical nutrition therapy interview frequency by gender are given in Table 2.

Table 2. Diet Self-Efficacy Scale Classification and Its Relationship with Educational Status, Age, Place of Residence and Medical Nutrition Therapy Interview Frequency by Gender									
	DIET SELF-EFFICACY SCALE CLASSIFICATION								
	Women (n=109)				**Men (n=41)**				
	Low		**High**		x^2 p	**Low**		**High**		x^2 p
	n	%	n	%		n	%	n	%	
Educational Status										
Primary school	35	61.40	22	38.60	x^2=10.585 p=0.014*	14	82.40	3	17.60	x^2=7.132 p=0.068
Secondary school	9	69.20	4	30.80		5	71.40	2	28.60	
High school	7	30.40	16	69.60		7	58.30	5	41.70	
Undergraduate and above	5	31.30	11	68.80		1	20.00	4	80.00	
Age (year)										
18-24	2	100.00	0	0.00	x^2=8.614 p=0.072	0	0.00	0	0.00	x^2=3.895 p=0.143
25-30	0	0.00	2	100.00		0	0.00	0	0.00	
31-37	1	33.30	2	66.70		1	100.00	0	0.00	
38-50	9	34.60	17	65.40		3	37.50	5	62.50	
51-64	44	57.90	32	42.10		23	71.90	9	28.10	
Place of Residence										
City	36	45.00	44	55.00	x^2=4.894 p=0.027*	12	52.20	11	47.80	x^2=4.360 p=0.037*
Rural	20	69.00	9	31.00		15	83.30	3	16.70	
Medical Nutrition Therapy Interview Frequency										
No	20	58.80	14	41.20	x^2=3.398 p=0.183	11	64.70	6	35.30	x^2=2.014 p=0.365
1 time	22	56.40	17	43.60		14	73.70	5	26.30	
>1 time	14	38.90	22	61.10		2	40.00	3	60.00	
0-1500 points: low self-efficacy level, 1500+ points: high self-efficacy level. In-group analysis: chi-square test analysis. p * <0.05										

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A significant difference was found between the DSES classifications of women and their educational status and place of residence and only place of residence among men (p<0.05). There was no significant difference between the total score of the diet self-efficacy scale and the BMI of the individuals by gender (p>0.05).

In women, a significant difference was found between total DSES and age only (p <0.05) while a significant difference was found between the total score of DSES and waist circumference for men (p< 0.05).

The total score of the DSES showed that while a negative significant correlation was found between the age (p<0.05), a significant positive correlation was found between the educational status (p<0.01).

A significant difference was found between the scores obtained from all sections and the total of the NLATA (p<0.001). Evaluation of DSES scores according to the nutrition literacy levels of the participants is given in Table 3.

A significant difference was found between the total scores of DSES (p<0.05). A significant difference was found between the nutrition literacy levels and DSES scores determined according to the score obtained from the general nutritional information section of the participants (p<0.05). There were significant differences between the nutrition literacy levels and DSES scores determined according to the score obtained from the reading comprehension section; the food groups section; the portion quantities section; the numeracy literacy and food label reading section (p<0.05 for all). A very significant positive correlation was found between the total DSES scores of the individuals participating in the study and the sections and the total scores of NLATA (p<0.001). While a moderate positive correlation was found between total DSES score and NLATA total and portion amounts section scores, a weak relationship was found between other departments (p<0.001).

Table 3. Evaluation of diet self-efficacy scale scores according to the nutritional literacy levels of the participants					
	Nutrition Literacy Assessment Tool in Adult Total Score				
	Insufficient¹ Mean±SD	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	561.91±212.22	1413.84±674.39	1789.64±662.50	x^2=46.920 p=0.000*	p^1-2=0.000* p^1-3=0.000* p^2-3=0.002*
	General Nutritional Information Section Score				
	Insufficient¹ Mean±SD	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	917.78±556.91	1197.74±702.50	1777.86±647.85	x^2=31.971 p=0.000*	p^1-2=0.091 p^1-3=0.000* p^2-3=0.000*
	Reading Comprehension Section Score				
Diet Self-Efficacy Scale Total Score	**Insufficient¹ Mean±SD**	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	1026.15±544.85	1494.62±751.67	1755.59±711.55	x^2=27.997 p=0.000*	p^1-2=0.002* p^1-3=0.000* p^2-3=0.092
	Food Groups Section Score				
	Insufficient¹ Mean±SD	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	929.31±765.32	1536.40±636.82	1561.15±692.34	x^2=19.508 p=0.000*	p^1-2=0.001* p^1-3=0.000* p^2-3=0.921
	Portion Quantities Section Score				
	Insufficient¹ Mean±SD	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	1168.69±716.23	1692.22±545.23	1948.10±733.13	x^2=27.524 p=0.000*	p^1-2=0.000* p^1-3=0.000* p^2-3=0.117
	Numeracy Literacy and Food Label Reading Section Score				
	Insufficient¹ Mean±SD	**Borderline² Mean±SD**	**Sufficient³ Mean±SD**	**Kruskal Wallis Test**	**Mann Whitney U test**
	1338.81±701.38	1774.00±679.67	1842.86±1087.61	x^2=8.953 p=0.011*	p^1-2=0.005* p^1-3=0.198 p^2-3=0.721
Intergroup analysis: Kruskal Wallis Test. Multiple comparisons: Mann Whitney U test. * p <0.05					

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DISCUSSION

Age and gender are considered as unchangeable risk factors and there is a risk for developing CVD in men over 45 years old and in women over 55 years old (10). In "Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment (TRANSCEND)" studies (9.378 women and 22.168 men) 31.000 patients were followed for an average of 56 months and women were found to have an average of 20 % less risk than men (11). In the study of Assessment of Factors Affecting Cardiovascular Diseases and Comparison of Cardiovascular Risk Scores conducted by Dülek et al. (12), the risk in men was found to be statistically significantly higher than in women. In the Primary Care Health Service Chronic Disease Monitoring Field Application Study; it is found that 50.00 % of the participants in the study were between 40-54 years old and 70.00 % were women (13). When the cardiovascular risk assessment data were analyzed by gender, 42.60 % of men were in the high and very high-risk group, while this ratio was 19.70 % in women and this difference was statistically significant. Our study was similar in terms of the participants' distribution of gender and mean age. As stated in the Primary Care Health Service Chronic Disease Monitoring Field Application Study, the number of men participants were relatively low and the average age of the men was higher than the women, and it is thought that the fact that men apply less to health centers because they work at the ages when they are "active" may be related to their early retirement and more frequent post-retirement (13).

Nutrition literacy, besides the ability to obtain and understand nutritional information, is the state of having the ability to make the appropriate nutritional decisions. Individuals with sufficient nutrition literacy levels have basic nutritional knowledge and have the skills to understand information about food items and food groups; read food labels, and control portion sizes (6,14). Individuals treated with MNT for CVD or risk factors need to know the content of the nutrients in their diets; be able to control portion sizes and make appropriate food and/or food product preferences by reading the labels (14). Costarelli et al. (15) found the mean total scores of nutrition literacy scales as 22.11 ± 5.67 and sufficient nutrition literacy levels (89.20 % of the participants) among Greek adults with chronic diseases in 2019 while we found our participants' nutrition literacy levels as borderline. One of the reasons for the difference between the findings may be that Costarelli et al. worked with a sample with a lower

average age (44.52 ± 17.44 years), and educational status may be one of the reasons for this difference. There are a limited number of studies examining the relationship between nutrition literacy and educational status. In a study conducted by Aihara and Minai (16) on the barriers of nutrition literacy among the elderly Japanese people; low educational status was associated with limited nutrition literacy among women and we found a very significant strong correlation between nutrition literacy levels and education in men and women participants (p <0.01). As the participants' educational levels increased, their nutrition literacy levels were also increased.

Nutritional information assessment is a significant component in nutritional research and is a prerequisite for the implementation of many policies and programs aiming at improving eating behavior (17). We found no significant relationship between previous medical nutrition therapy and the level of nutritional knowledge. This may be due to the effectiveness of medical nutrition therapy or the fact that nutrition education has not been given to the patient in the context of medical nutrition therapy.

Literacy skills are significant determinants of health and affect individuals' ability to prevent, manage and treat disease (18). Diet compliance is important for a healthy lifestyle. Individuals must demonstrate determination and individual competence to comply with diet (8). Self-efficacy belief is called the belief that "the individual can organize and successfully perform the activity necessary to perform a certain performance". It can be said that the individual self-efficacy belief in the conduct of behavior affects and directs the behavior. This "I can do it belief" reflects the feeling of controlling the conditions and if the individual believes that he/she can achieve results then determines the course of his life by acting more actively. According to the self-efficacy theory, if the individual believes that he/she can reach a result, he acts more actively and can control life (8,19).

Self-efficacy of patients is very important in controlling heart disease and preventing risk factors, which is the number one cause of death in our country and the world, and which requires diet. The dietary self-efficacy level of individuals shows their ability to create behavior change and follow the diet. It is thought that nutrition education can be shaped according to the diet self-efficacy level of individuals. It is anticipated that if the self-efficacy of the patients is low, nutrition education to be provided can be enriched by providing the necessary motivation and by

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offering solutions to the problems of the individuals, thus increasing the self-efficacy belief of the patient and ensuring compliance with the diet (8). In this study, according to the diet self-efficacy levels of the participants; nutrition literacy levels and components of nutrition literacy; general nutritional knowledge, reading comprehension skills, food groups information, portion quantities information, and numeracy literacy and food label reading skill levels were analyzed by inter-group analysis, and a significant difference was found between all parameters (p <0.05). Participants with a high level of diet self-efficacy were found to have significantly higher levels of nutrition literacy, general nutritional knowledge, reading comprehension, food groups information, portion quantities information, numeracy literacy, and food label reading skills.

CONCLUSION

Our results emphasize the importance of medical nutrition therapy in the management of cardiovascular disease and risk factors, the necessity of organizing medical nutrition therapy for these individuals by a dietician, and providing nutrition education to individuals the scope of medical nutrition therapy. As a result of the study, "as the nutrition literacy levels of individuals increase, dietary self-efficacy levels also increase". According to this result, it is recommended to determine the nutrition literacy levels of individuals and organize nutrition education to increase the nutrition literacy levels of individuals. It is also emphasized that nutrition education aimed at increasing the nutrition literacy level can increase the success rate of medical nutrition therapy by increasing the diet self-efficacy levels, which are the indicators of individuals' behavior change capacity.

DECLARATIONS

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Conflicts of Interest/Competing Interests
The authors declare no conflicts of interest to disclose.

Ethics Approval
This study was performed with the ethical approval of the Yeditepe University Clinical Research Ethics Committee dated 07.11.2019 after obtaining the necessary permissions from Isparta Provincial Health Directorate. The authors declare that all experiments on human subjects were conducted following the Declaration of Helsinki and that all procedures were carried out with the adequate understanding and written consent of the subjects.

Availability of Data and Material
We can provide the original data

Authors' Contributions
Kübra Kazak: Conception and design of the study; generation, collection, assembly, analysis and interpretation of data; and drafting or revision of the manuscript; approval of the final version of the manuscript; Binnur Okan Bakır: Conception and design of the study; and drafting or revision of the manuscript; approval of the final version of the manuscript.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nutrition and Dietetics / Beslenme ve Diyetetik

Can Online Dietitian Be a Novel Trend of Post-Pandemic Era in Turkey?

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Özge ÇONAK

ABSTRACT

Purpose: The aim of this study was to investigate weight management-related Google search trends in Turkey prompted by the pandemic.

Methods: Keywords were "diet", "dietitian", "body mass index", "exercise", "calorie", "weight gain", "healthy nutrition", "weight loss", "fat burning", "slimming", "online diet" and "online dietitian". Data collection and time series analysis were completed using the 4.1.0 version of the R Studio program and its gtrendsR, ggplot2, prophet, dplyr, forecast and ggforce packages. SPSS software version 17 was used for statistical analysis of keyword relative search volumes (RSVs) during the prepandemic, early pandemic and late pandemic periods.

Results: The RSV of "dietitian" keyword was significantly higher in the late pandemic period than in the early pandemic period *(p< 0.05)*. "Exercise" and "online diet" keywords had significantly higher RSVs in the early pandemic period than in the prepandemic period *(p< 0.05)*. The search queries for "healthy nutrition" were significantly lower in the late pandemic period than in the prepandemic period *(p< 0.05)*. According to the search volume for the previous 10 years, the predicted search trends of "body mass index", "exercise", "healthy nutrition", "online diet" and "online dietitian" tended to increase depending on the seasonal search profile.

Conclusion: A large increase in actual and predicted search queries of "online dietitian" can provide some cues about public tendencies in the postpandemic era in Turkey. Some guidelines, including web-based communication competencies in dietitian-patient relationships and follow-ups of the diet on the online platform, should be published for the postpandemic period by authorities.

Keywords: body weight, coronavirus, diet, nutritionist, pandemic

Çevrimiçi Diyetisyenlik Türkiye'de Pandemi Sonrası Dönemin Yeni Akımı Olabilir Mi?

ÖZET

Amaç: Bu çalışmanın amacı, pandemiyle tetiklenen ağırlık yönetimi ile ilgili Türkiye'deki Google arama trendlerini araştırmaktır.

Yöntemler: Anahtar kelimeler "diyet", "diyetisyen", "vücut kitle indeksi", "egzersiz", "kalori", "kilo alımı", "sağlıklı beslenme", "kilo verme", "yağ yakma", "zayıflama", "online diyet" ve "online diyetisyen" di. Veri toplama ve zaman serisi analizi, R Studio programının 4.1.0 sürümü ve bu sürümün gtrendsR, ggplot2, Prophet, dplyr, tahmin ve ggforce paketleri kullanılarak tamamlandı. Anahtar kelimelerin pandemi öncesi, erken pandemi ve geç pandemi dönemlerinde göreli arama hacimlerinin (GAH'ler) istatistiksel analizi için SPSS yazılımı sürüm 17 kullanıldı.

Bulgular: "Diyetisyen" anahtar kelimesinin GAH'ı geç pandemi döneminde erken pandemi dönemine göre anlamlı ölçüde daha yüksekti *(p< 0.05)*. "Egzersiz" ve "online diyet" anahtar kelimeleri erken pandemi döneminde pandemi öncesi döneme göre anlamlı ölçüde daha yüksek GAH'lara sahipti *(p< 0.05)*. "Sağlıklı beslenme" için yapılan arama sorguları, pandemi döneminin sonlarında, pandemi öncesi döneme göre anlamlı ölçüde daha düşüktü *(p< 0.05)*. Son 10 yıldaki arama hacmine göre, "vücut kitle indeksi", "egzersiz", "sağlıklı beslenme", "online diyet" ve "online diyetisyen" arama trendleri, mevsimsel arama profiline bağlı olarak artma eğilimindeydi.

Sonuç: "Online diyetisyen" için gerçek ve tahmin edilen arama sorgularındaki büyük artış, Türkiye'de pandemi sonrası dönemde halkın eğilimleri hakkında bazı ipuçları verebilir. Pandemi sonrası dönem için diyetisyen-hasta ilişkilerinde web tabanlı iletişim yetkinlikleri ve diyetin online platformda takibi gibi bazı kılavuzların otoritelerce yayınlanması gerekmektedir.

Anahtar Kelimeler: vücut ağırlığı, koronavirüs, diyet, diyetisyen, pandemi

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Coronavirus disease (COVID-19) has become a global public health concern caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to the easy transmission of SARS-CoV-2 from human to human, the number of coronavirus cases has dramatically reached the alert level around the world, with a huge pandemic in Turkey (1).

Obesity is another serious public health concern worldwide and in Turkey. According to the European Health Interview Survey in 2014, Turkey is ranked among the top countries in Europe in terms of obesity, with a prevalence of 19.9% (2). Obesity causes an increased risk of noncommunicable diseases, such as type 2 diabetes, cardiovascular disease, hypertension and some cancers as well as increased rates of mortality. Obese individuals can suffer from metabolic dysfunctions, alterations in immune responses, pneumonia development, respiratory tract infections, abnormalities in the inflammatory process and mortality from critical inflammation (3). For these reasons, obesity is considered a risk factor for severe COVID-19 complications (4). Consistently, a systematic review and meta-analysis showed that obesity increased the risk of hospitalization, mechanical ventilation and disease severity in coronavirus (5). Similarly, the outcomes of Cornejo-Pareja et al.'s study showed that long-term complications of COVID-19 could appear more frequently and severely in obese patients (6).

To avoid obesity, behavioral treatments are regarded as preventive care and viable strategies during the outbreak. Rychter et al. strongly advised that each COVID-19 patient should complete the measurement of body weight to avoid obesity-related infections and mortality. Moreover, they emphasized the requirement of nutritional and behavioral guidelines for obese COVID-19 patients (7).

Google trends (GT) studies are commonly carried out to determine the public interest during pandemic conditions. It provides the search queries as the RSV of any keyword in a certain region for a specific time period. During the outbreak, researchers have addressed public interest in coronavirus, immunity, diet, foods, exercise, nutrients, specific disorders, lockdown and hygiene-related keywords around the world (8–11). McCarty and McGoldrick demonstrated that diabetes and weight loss keywords had significantly increased in search volume during the outbreak around the world. They suggested a potential relationship between metabolic health and the COVID-19 outbreak (9). On the other hand, the search profile could

vary from one country to another. Although both coronavirus and obesity have appeared with a huge prevalence in Turkey, no detailed infodemiological analysis about the weight management-related internet queries in Turkey during the pandemic could be found.

This paper aimed to evaluate weight management-related web-based searches of internet users in Turkey. In addition, the RSVs of the prepandemic, early pandemic and late pandemic periods were compared. Additionally, potential search profiles of keywords were estimated for the future.

MATERIALS AND METHODS

Study Design
This research is an infodemiological study that was carried out with retrospective data between 2011 and 2021 of the GT search engine (https://trends.google.com) (12). Data about search queries can be obtained as RSVs from GT. RSV can be expressed from 0 to 100, depending on search interest ranking (13).

In this study design, the search region was "Turkey", so searches were completed in the Turkish language. Keywords were "diet", "dietitian", "body mass index", "exercise", "calorie", "weight gain", "healthy nutrition", "weight loss", "fat burning", "slimming", "online diet" and "online dietitian".

Data Collection
Data collection and time series analysis were carried out with the usage of the 4.1.0 version of the R Studio program and the gtrendsR, ggplot2, prophet, dplyr, forecast and ggforce packages of this program (R statistical software, www.R-project.org). In this context, the "gtrendsR" package was used to display the trends over time, which are also known as hits and geographic representations of query results. The grendsR package in the R program provides an interface to retrieve and view information returned online (14). The "ggplot2" package was used to determine how to map variables to aesthetics and which graphic principles to use (15). The "prophet" package was used to estimate further trends. The "prophet" package in the R program performs a procedure to predict the time series data based on an additional model where nonlinear trends are suitable for annual, weekly, and daily seasonality, as well as holiday effects (16). The dplyr package was used to create the data frames quickly and consistently, both in memory and nonmemory objects (17). The "forecast" package in the R program was used to provide methods and tools to display and analyze the univariate

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time series forecasts, including exponential smoothing through state space models and automatic ARIMA modeling (18). The "ggforce" package gives the search trends of certain periods within the search spectrum more closely. Therefore, the "ggforce" package was used to zoom in on ggplot plots for specific time periods (19).

In addition to time series analysis, we focused on the three periods of the pandemic within the scope of the study. These periods were the prepandemic period *(January 1, 2019 – June 1, 2019)*, early pandemic period *(January 1, 2020 – June 1, 2020)* and late pandemic period *(January 1, 2021 – June 1, 2021)*. The prepandemic period is important to compare the public interests before the pandemic and pandemic periods. The early pandemic period can represent the effect of strict pandemic conditions on the public in terms of lockdown, anxiety and uncertainty. The late pandemic period can be an indicator of the postpandemic process and new lifestyle conditions.

Statistical Analysis
SPSS software version 17 was used for statistical analysis of the prepandemic, early-pandemic and late-pandemic periods (SPSS Inc., Chicago, Illinois, USA). After the data were drawn with the R program from GT via gtrendsR, the consistency was tested for each keyword according to the inter-periods search volumes with the Friedman test. The Friedman test is a nonparametric test used for repeated measurements (20). The confidence interval was selected as 95%. p < 0.05 was accepted as significant in the tests.

The consistency level of search volumes was calculated by Kendall's W test as Kendall's coefficient of concordance (W). W ranges from 0.00 and 1.00 (0.00–0.20 very weak consistency, 0.21–0.40 weak consistency, 0.41–0.60 medium consistency, 0.61–0.80 strong consistency and 0.81–1.00 a very strong consistency) (21). The Wilcoxon rank sum test was used to compare the RSV means of two different periods. Analysis results were drawn as bar graphs by GraphPad Prism 9.

RESULTS

We focus on the public interest profile of keywords in the early-pandemic period within the spectrum of the previous 10-year period in Figure 1. Accordingly, the RSV trends of "dietitian", "body mass index", "weight gain" and "slimming" dramatically decreased in the first months of the early-pandemic period but later increased. The amounts of increase and decrease in the search queries were approximately equal to each other. The RSVs of "exercise" greatly increased in the first months of the early-pandemic period but later slightly decreased.

"Diet", "calorie", "weight loss" and "fat burning" keywords' RSVs had gradually increasing search profiles with slight fluctuations at the beginning of the lockdown. On the other hand, "healthy nutrition" keyword RSVs gradually decreased the search profile with slight fluctuations. Last, "online diet" and "online dietitian" keywords' RSVs peaked two times within the early-pandemic period (Figure 1).

According to the Friedman test, the search queries of only "healthy nutrition" keywords were determined to be significantly consistent between periods *(p< 0.05)*. Kendall's W test showed that there was moderate consistency of "dietitian", "exercise", "calorie" and "online diet"' RSV data during the selected periods (Kendall's coefficient of concordance score: 0.41–0.60). In addition, there was strong consistency in the "healthy nutrition" keyword RSVs during pandemic-related periods (Kendall's coefficient of concordance score: 0.61–0.80) (Table 1).

Wilcoxon rank sum test findings demonstrated that the mean RSV of the "dietitian" keyword was significantly higher in the late-pandemic period than in the early-pandemic period *(p< 0.05)*. The mean RSV of the "exercise" keyword in the early-pandemic period was significantly increased compared to that in the prepandemic period *(p< 0.05)*. This increased profile of "exercise" keywords continued during the late-pandemic period, but it was not statistically significant (p= 0.08). In addition, the mean RSV of the "calorie" keyword in the late-pandemic period was significantly higher than that in the prepandemic period *(p< 0.05)*. The average RSV of the "calorie" keyword was higher in the late pandemic than in the early-pandemic period, but it was not statistically significant (p= 0.08) (Figure 2a).

The mean search query of the "healthy nutrition" keyword was significantly lower in the late- pandemic period than in the prepandemic period *(p< 0.05)*. In addition, the mean RSV of "healthy nutrition" was higher in the early-pandemic period than in the late-pandemic period, but the difference was not statistically significant. The mean RSV of the "online diet" keyword was significantly higher in the early-pandemic period than in the prepandemic period *(p< 0.05)*. Last, the average RSV of the "online dietitian" keyword was higher in the late-pandemic period than in the prepandemic period, but the difference was not statistically significant (p= 0.08) (Figure 2b).

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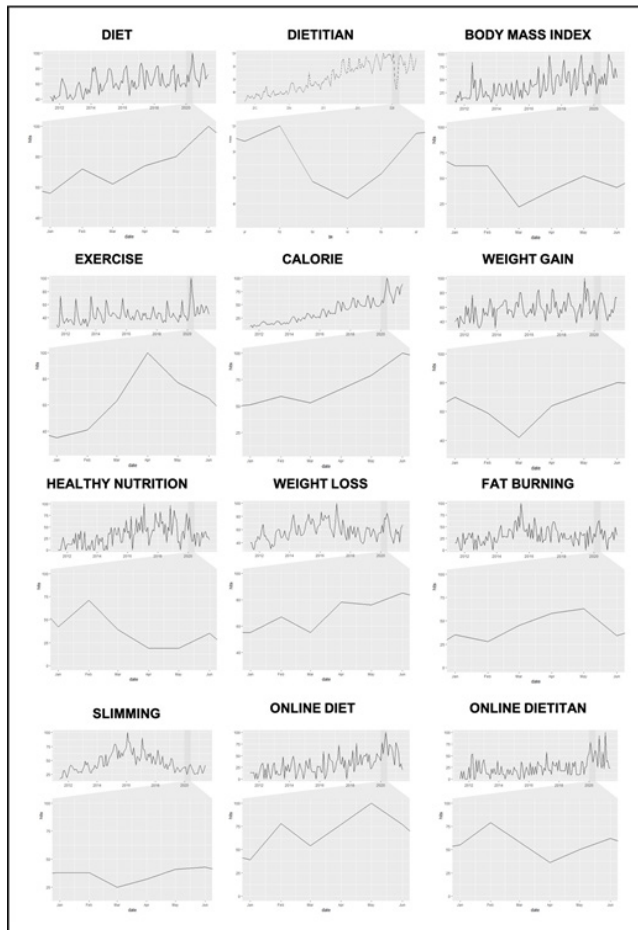
Figure 1. The public interest profile of keywords in the early-pandemic period within the spectrum of the previous 10-year period.

Figure 2. a) Wilcoxon rank sum test results of "diet", "dietitian", "body mass index", "exercise", "calorie" and "weight gain" keywords' RSVs during the pre-pandemic, early-pandemic and late-pandemic periods.
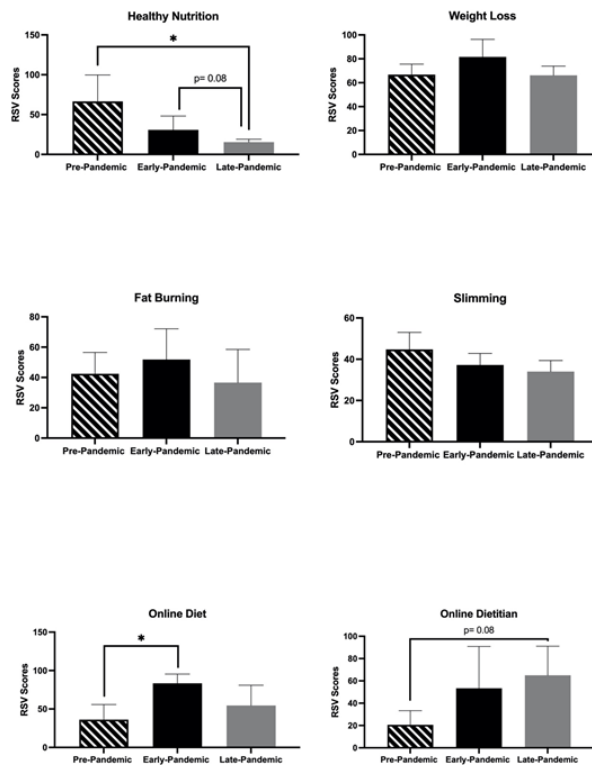
Figure 2 b) Wilcoxon rank sum test results of "healthy nutrition", "weight loss", "fat burning", "slimming", "online diet" and "online dietitian" keyword RSVs during the pre-pandemic, early-pandemic and late-pandemic periods.

Table 1. Friedman X² and Kendall's W analysis results of keyword RSVs during the pre-pandemic, early-pandemic and late-pandemic periods			
Keywords	**Friedman X²**	**p**	**Kendall's W**
Diet	0.105	0.940	0.011
Dietitian	6.000	0.05	**0.600**
Body Mass Index	1.600	0.449	0.160
Exercise	5.200	0.074	**0.520**
Calorie	6.000	0.05	**0.600**
Weight Gain	2.842	0.241	0.284
Healthy Nutrition	6.400	**0.041**	**0.640**
Weight Loss	1.600	0.449	0.160
Fat Burning	0.400	0.819	0.040
Slimming	2.800	0.247	0.280
Online Diet	5.200	0.074	**0.520**
Online Dietitian	1.200	0.549	0.120

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Figure 3 shows the predicted search profile of keywords for further periods. According to the search volume for the previous 10 years, the predicted search trends of "diet", "dietitian", "calorie", "weight gain" and "slimming" tended to greatly increase or decrease in the future when compared to the actual statement. The predicted search trends of "body mass index", "exercise", "healthy nutrition", "online diet" and "online dietitian" tended to increase depending on the limits of seasonal search trends in the future. In addition, the predicted search trends of weight loss mostly tended to be similar to their seasonal search trend for further periods.
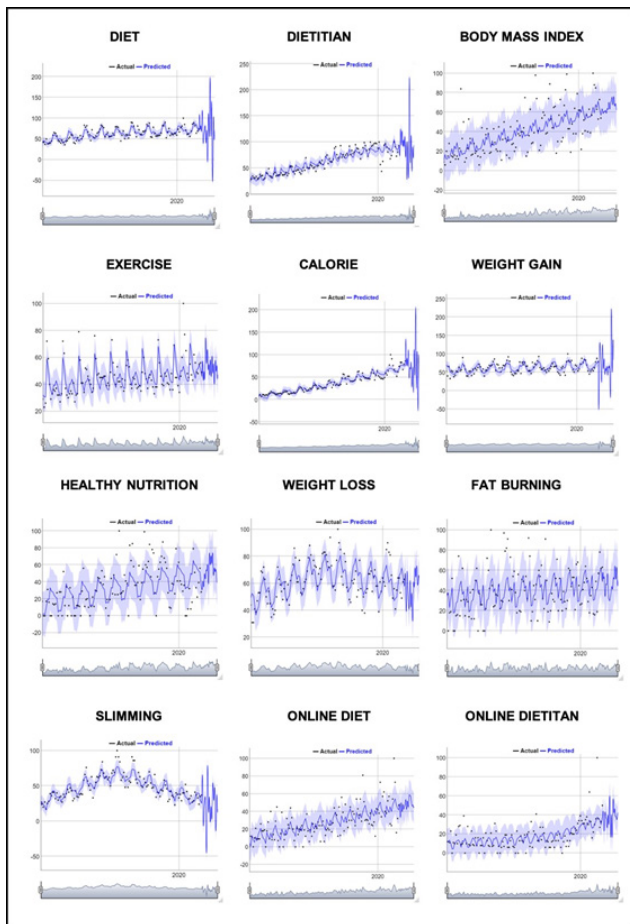
Figure 3. The previous 10 years' search data and predicted search profile of keywords for further period.

DISCUSSION

In our study, the search volumes of "dietitian", "body mass index", "weight gain" and "slimming" keywords sharply dropped, whereas those of "diet", "calorie", "weight loss" and "fat burning" slightly dropped in the first months of the early-pandemic period. In the literature, similar

findings were reported on a global scale. In this context, Ngoc and Kriengsinyos investigated the global search interests of "calorie", "weight loss", "weight gain" and "aerobic exercise" keywords from January 1, 2018 to December 13, 2020. Accordingly, the pandemic has significantly changed individual weight-related concerns. Consistent with our findings, global interest regarding "calorie", "weight loss" and "weight gain" dropped during the first month of the lockdown period (11). The global search profile of these keywords was quite similar to the search interests in Turkey for the same period.

In addition, "online diet" and "online dietitian" keywords' RSVs peaked two times within the early-pandemic period. No infodemiological data on this subject have been reported in previous studies. However, in some studies conducted in different countries, it was noted that similar practices were used during this period. For instance, in a study conducted with Canadian dietitians, online and telephone interviews were mentioned during the pandemic period. It was stated that these interviews had successful results in some patients, but people with low socioeconomic status did not have these technologies (22).

It is well known that nutritional status and physical activity are closely related to public health and disease processes. In this context, to effectively combat COVID-19 in patients with optimal body weight, healthy lifestyle activities, such as exercise during free time, maintaining a healthy body weight, ingesting sufficient fruit and vegetables and avoiding ultra-processed food consumption, should be performed (23). However, it is emphasized that unhealthy eating habits have become widespread in studies carried out in Turkey during the quarantine period (24-25). Consistently, "healthy nutrition" keyword RSVs gradually decreased in their search profile with slight fluctuations.

The reason for the significantly higher mean RSV of the "dietitian" keyword in the late-pandemic period than in the early-pandemic period can be related to increased weight gain due to lockdowns *(p< 0.05)*. The interest in the "dietitian" keyword of internet users suddenly decreased in the first months of the early-pandemic period. This situation confirmed the reduced interest of the public in weight management strategies, so weight gain may have increased in the early-pandemic process. Therefore, people who gained weight in the early-pandemic period may have wanted to lose weight in the late-pandemic period.

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Being physically active plays a significant role in weight control, maintaining immune competence, reducing the risk of illness. The lockdown process causes more difficulty in the sustainability of the physical activity schedule (26). In our study, the search volume of the "exercise" keyword dramatically increased at the beginning of the early-pandemic period but later slightly decreased. Nevertheless, it had significantly higher search queries in the early-pandemic period than in the prepandemic period *(p< 0.05)*. We considered that this could be related to it covering home-based exercise due to lockdowns. Similarly, Mayasari et al. showed that worldwide RSVs of "exercise" keywords were positively correlated with COVID-19 daily confirmed cases (rs: 0.599, *p< 0.001*) and COVID-19 cumulative confirmed cases (rs: 0.611, *p< 0.001*) (10).

Whereas the mean RSV of the "calorie" keyword significantly increased from the prepandemic period to the late-pandemic period, the average RSV of the "healthy nutrition" keyword significantly decreased *(p< 0.05)*. This situation can be explained by the fact that people may focus on short-term targets instead of long-term targets due to psychological issues during the pandemic.

In this study, the average RSV of the "online diet" keyword was significantly higher in the early-pandemic period than in the prepandemic period *(p< 0.05)*. However, search queries about "online diet" slightly decreased in the late pandemic period. On the other hand, the average RSV of the "online dietitian" keyword increased gradually during the prepandemic and late-pandemic periods, but this elevation was not statistically significant (p= 0.08). Nevertheless, this increase is expected to continue for postpandemic periods, so it can be a novel trend of the public as a weight management strategy in Turkey. In that context, the pandemic process may be an opportunity for new mode of working in the dietetic profession. However, the success of nonverbal communication in the dietetic profession should be questioned at this point. The success of online diet intervention programs depends on various factors, such as participant-related parameters, intervention programs and the efficiency of interventions (27).

In fact, it was interesting that although "online diet" searches decreased in the late-pandemic period, "online dietitian" searches steadily increased. This may be because the online diet includes programs that are created with artificial intelligence and do not require any professional follow-up. Similar programs may be less successful in weight management than professional follow-up via online dietitian, and this situation could give rise to a drop in the search queries of the "online diet" keyword. In the literature, Beleigoli et al. investigated the effect of a 24-week personalized web-based weight loss behavior change program with and without dietitian online coaching on overweight and obese adults. They suggested that engagement with the program was higher in the platform-plus coaching group than in the platform-only group. They claimed that platform-plus coaching was related to a significantly greater chance of weight loss that is clinically meaningful (28).

This study includes some cues about web-based search volumes of weight management-related keywords for the postpandemic process through predicted search profiles. According to the previous 10 years of data, there were no certain estimations about future search queries of "diet", "dietitian", "calorie" and "slimming" keywords. This situation could be explained by their previous RSVs being suddenly up and down due to external factors while having a regular search profile. These keywords may be searched a lot or not at all in the future depending on any factor. On the other hand, although "body mass index", "exercise", "healthy nutrition", "online diet" and "online dietitian" keywords had high or low RSV values at many times within the search spectrum, it is predicted that their future search queries can increase within the seasonal search profile in the future. The reason is that their predicted search trends for previous years tend to increase regularly and gradually. Last, as the seasonal search trend of the "weight loss" keyword has had a similar profile in the last 10 years, it may be predicted that its seasonal search trend can be similar in the future. The search queries about "weight loss" cannot be greatly affected by external factors.

This study has some strengths when compared to other infodemiological studies in the literature. First, other studies included only statistical analysis of retrospective data in some countries during the pandemic. This study found both current and predicted search volumes and statistical analysis of selected keywords. Second, other infodemiological studies have investigated global public interest in some weight-related issues during the pandemic. In addition to these keywords, our study also analyzed "diet", "dietitian", "online diet" and "online dietitian", and these keywords have vital importance in terms of understanding public preferences about professional weight management strategies for the postpandemic process.

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There are several limitations in this retrospective infodemiological study such as unknown of sociodemographic properties of participants, carried out only Turkey, limited with certain time period and linguistic restrictions.

CONCLUSION

In this study, a large increase in search queries about online dietitians in both actual and predicted data can provide an explanation of public orientation for the postpandemic era in Turkey. Even if the pandemic ends one day, its impacts on individuals' lives, behavior and habits can continue. Effective use of online platforms as professionals can be one of these impacts. In this context, guidelines that include web-based communication competencies in dietitian-patient relationships and follow-up of the diet on the online platform should be provided to regulations to effectively combat obesity in the postpandemic period. This public interest may lead to diet monitoring by nonprofessionals, and diets touted by nonprofessionals can threaten public health. Therefore, some authorities should develop policies that control whether the specialist is a dietitian on web-based platforms. Moreover, it should also be taken into account in the planning of nutrition and dietetic education for technology embracement and new opportunities for the future. In this way, it can be ensured that the public can access accurate and reliable information from professional dietitians.

DECLARATIONS

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This study has not been funded by any institution.

Conflict of Interest
All authors declare that they have no conflicts of interest.

Ethics Approval
This study did not require ethical committee approval.

Availability of Data and Material
We can share the all data of the study.

Authors' Contributions
E.G. designed and coordinated the study and wrote the manuscript; Ö.Ç. collected the data, performed statistical analyses and revised the manuscript.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

The Mediating Role of Role Overload in the Effect of Role Conflict and Role Ambiguity on Work Harassment

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ABSTRACT

Purpose: The purpose of this study is to determine the effects of role ambiguity and role conflict on workplace harassment and the intermediary role of role overload in this effect. The literature includes no research on the relationship between nurses' workplace role ambiguity, role overload, role conflict and workplace harassment. The study used role overload as a mediating variable, which adds to the originality of the study.

Methods: The study used a cross-sectional research design and surveyed 260 nurses working in a public hospital in Turkey. The data were analyzed using descriptive statistical methods, Pearson correlation analysis and Hayes Macro regression.

Result: Role ambiguity has no direct or indirect effect on workplace harassment. On the other hand, role conflict affects workplace harassment directly and indirectly through role overload.

Conclusion: In line with these results reveal that nurses who are harassed in the workplace should take precautions against role conflict and increased role load. The results of the research reveal that nurses who experience workplace harassment in particular need to take precautions against increased role conflict and role overload.

Keywords: Healthcare, Workplace Harassment, Health services, Violence

Rol Çatışması ve Rol Belirsizliğinin İş Tacizi Üzerindeki Etkisinde Aşırı Rol Yükünün Aracı Rolü

ÖZET

Amaç: Bu çalışmanın amacı, rol belirsizliği ve rol çatışmasının işyeri tacizi üzerindeki etkilerini ve bu etkide aşırı rol yükünün aracı rolünü belirlemektir. Literatürde hemşirelerin iş yeri rol belirsizliği, rol aşırı yüklenmesi, rol çatışması ve işyeri tacizi arasındaki ilişkiye dair herhangi bir araştırma bulunmamaktadır. Çalışmada, aşırı rol yükü aracı değişken olarak kullanmış ve bu da çalışmanın özgünlüğünü artırmıştır.

Yöntem: Kesitsel bir araştırma deseninde olan araştırmada Türkiye'de bir kamu hastanesinde çalışan 260 hemşire ile anket yapılmıştır. Veriler, tanımlayıcı istatistiksel yöntemler, Pearson korelasyon analizi ve Hayes Macro regresyon kullanılarak analiz edilmiştir.

Bulgular: Rol belirsizliğinin işyeri tacizi üzerinde doğrudan veya dolaylı bir etkisi yoktur. Öte yandan, rol çatışması, işyerinde tacizi doğrudan ve dolaylı olarak rol aşırı yüklenmesi yoluyla etkilemektedir.

Sonuç: Bu sonuçlar doğrultusunda işyerinde tacize uğrayan hemşirelerin rol çatışmasına ve artan rol yüküne karşı önlem alması gerektiği ortaya çıkmaktadır. Araştırma sonuçları, özellikle işyeri tacizi yaşayan hemşirelerin artan rol çatışması ve aşırı rol yüküne karşı önlem almaları gerektiğini ortaya koymaktadır.

Anahtar Kelimeler: Sağlık, İşyeri Taciz, Sağlık hizmetleri, Şiddet

Nurses are directly and indirectly involved in providing health services in an effective, efficient and uninterrupted manner. For this reason, nurses are one of the valuable resources of the health sector. It is becoming even more valuable for countries with low numbers of active working nurses, such as Turkey (1). The low number of nurses increases the number of patients per nurse who need to be cared for and the quality of nurse care is deteriorating (120% missed care; 20% task-in-queue time) and the role overload is increasing due to the increasing number of patients (2). The increased role overload is associated with anxiety, depression, anger and job dissatisfaction (3). Apart from these negative consequences, role overload is among the precursors of workplace harassment (4). Recent studies have revealed that nurses are subjected to high rates of harassment at work (min. 38.6% – max. 86%) (5). Studies on workplace harassment experienced by nurses at work and the effects of workplace harassment show that there are individual and organizational negative effects of workplace harassment. Headache, insomnia, low motivation and depression symptoms are found in nurses exposed to this type of behavior at work (6). In organizational dimensions, however, nurses develop job dissatisfaction and intention to leave work (5) as well as displaying increased burnout levels (7) and decreased organizational commitment (8). In addition, the number of studies on variables causing workplace harassment is highly limited although there are studies on the consequences of exposure of nurses to workplace harassment, people inflicting violence, profiles of perpetrators and reactions of nurses to such behavior. Therefore, this study examines the intermediary role played by ambiguity, conflict and overload of nurses in terms of workplace harassment.

THEORETICAL FRAMEWORK

Role Overload
There are structures among role theories that are considered to be alternative structures for role overload and used synonymously with role stress factors. Role overload is considered to be one of them (9). Increased role overload is regarded as the degree to which someone perceives the number of commitments and responsibilities under time pressure. Precursors of role overload include organizational elements (mergers, downsizing, high performance standards, long working hours, night shifts etc.), cultural norms, technology, and information overload (10).

The number of patients, the need for care of patients, the characteristics of units or services, existing/used technologies, the knowledge and skills of nursing personnel are among the factors affecting the role overload of nurses (11). Insufficient number of nurses in meeting patient needs increases the role overload of nurses and negatively affects the actual level and quality of care provided for the patient (falling patients, decubitus, drug administration errors) (12).

Role Conflict
Role conflict occurs when an individual has two or more role requirements that overlap with each other. Role conflict increases when the works the employee needs to do are very different and unrelated, the employee has relations with different groups in the workplace, he or she receives incompatible demands, and when there are not enough personnel in the workplace. Especially in matrix organizations (hospital etc.), the breakdown of the chain of command and accountability to multiple authorities affect role conflict (13). Therefore, it is common to experience role conflict in health workers, especially nurses (14). The studies performed in Turkey suggested that nurses had a higher role conflict than other health workers.

Role Ambiguity
Role ambiguity refers to uncertainty about what needs to be achieved at work (15). Role ambiguity can be defined as a situation in which an individual has no clear knowledge of the requirements/methods of completing their work in relation to the job or role expectations in the organization. It occurs when the individual's duty or authority is not clearly defined or he or she refrains from taking responsibility for anything. According to the literature, role ambiguity of nurses are affected by age groups, educational status, professional experience, service periods at the hospitals where they work, units where they work, whether they choose their professions themselves, whether they find their profession suitable for them, vocational training and their perception of vocational competence (16).

The Intermediary Effect of Work Overload on Workplace Harassment Resulting from Role Conflict and Role Ambiguity
In the literature, role conflict is often treated as a workplace stress factor along with role uncertainty. However, research suggests that these variables have different origins and therefore require different management interventions. For this reason, these variables are not discussed together in the study. This topic was chosen because role conflict and role ambiguity variables are important in workplace harassment and there has been an increase in role overload in recent periods (17). Even if the literature

does not include a sample of nurses, it is possible to find a relationship between role ambiguity and workplace harassment (18). Role ambiguity experienced by nurses who are expected to work as members of a team in hospital organization could increase workplace harassment. The fact that nurses who experience role ambiguity become uncertain about what they need to achieve and do not know their role expectations will prevent them from developing a positive relationship with other nurses and their superiors.

The following hypothesis has been developed in line with this information:

H1: *Role ambiguity has a positive correlation with workplace harassment.*

Increased role conflict damages workplace relationships of nurses who need to work as a team. Nurses whose workplace relationships are damaged are expected to suffer from workplace harassment. In their study on health care workers, Balducci et al. (17) found that role conflict affects workplace harassment.

In the light of this expectation and information, the following hypothesis has been formed.

H2: *Role conflict has a positive correlation with workplace harassment.*

The role overload variable was used as the intermediary variable in the research. This is because Van den Brande et al. (19) identified role conflict, role overload, and role ambiguity as precursors of workplace harassment in their systematic review. Furthermore, high and increasing role overload is recognized as both the trigger and moderator of the work harassment process in the workplace (20).

As a result of this information, the following hypothesis has been developed:

H3: *Role overload plays an intermediary role in the effect of role conflict and role ambiguity on workplace harassment.*

METHODS

Design and Sample
A cross-sectional study was designed using a survey. The stratified sampling method was used based on the number of nurses working in hospitals when selecting samples from hospitals. A total of 790 nurses are employed at the three hospitals. A total of 260 nurses, including 181 from Sakarya University Education and Research Hospital, 57 from Yenikent State Hospital and 22 from Toyotasa Emergency hospital, participated in the study. 74.6% of the sample consisted of women and the average age was 33.11±7.05. 56% of the participants were undergraduates, 32.4% had associate degrees and 11.6% were high school graduates.

Instruments
Role Ambiguity and Role Conflict Scales: The Role Conflict Scale and the Role Ambiguity Scale that were developed by Rizzo et al. (13) and whose Turkish validity and reliability works were carried out by Ertam Eray (21) consist of 8 and 6 statements respectively. Low role ambiguity scores in the role ambiguity scale refer to high role ambiguity. The Cronbach Alpha coefficients of the role conflict and role ambiguity scales were 0.82 and 0.81 in the original 0.75 and 0.85 in the Turkish adaptation while these values were 0.85 and 0.84 for this study.

Role Overload Scale: The scale was developed by Beehr et al., (22) and its Turkish validity and reliability works were carried out by Akbolat et al. (23). The scale consists of three items. Two statements in the scale are negative (I have to work a lot harder so that I can fulfill my duties properly, and I never had enough time to do everything about my job.) while one statement is positive (The amount of work I am asked to do is fair). Higher scores in the scale mean higher role overload and lower scores mean lower role overload. The Cronbach-Alpha coefficient of the scale was 0.56 in the original, 0.75 in the Turkish version, and 0.71 in this study.

Work Harassment Scale-WHS: Developed by Bjorkqvis et al. (24), the Work Harassment Scale (WHS) consists of 24 statements aimed at questioning whether an individual has received personally humiliating or oppressive behavior from co-workers over the past 6 months. Validity and reliability analyses were conducted by adding two more items to the scale in the study carried out by Baguena et al. (25). According to this study, the scale consists of four factors. The first factor of the scale (social isolation) is called "attack on the victim's relationships", the second factor is "verbal assault"; the third factor is "attack on the victim's private life" and the last factor is "attack on the victim using organizational tools". The Cronbach-Alpha coefficient of the scale is 0.95 in the original, 0.92 in the Turkish adaptation and 0.94 in this study.

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Data Collection

The data were collected by the researchers using surveys in the three Hospital in Sakarya Turkey between November and October 2019. Moreover, the participants were given sufficient time to fill in the questionnaire (average 12 ± 2 min.). Finally, the questionnaire forms were collected by researchers in sealed envelopes to provide participants.

Ethical Considerations

Before the data was collected, permission was obtained from the General Secretariat of Sakarya Public Hospitals Association and a report on the compliance of the study with the ethical rules was obtained from Sakarya University Ethics Committee (Document no. 6192333/050.99/).

RESULTS

Descriptives and Correlations

Table 1 shows means, standard deviations and correlation values of the variables. Role ambiguity (2.52±0.703) and work harassment (0.64±0.645) have low means while role conflict (3.35±0.732) and role overload (3.48±0.747) have higher means. According to the results of the correlation analysis, role ambiguity has a negative correlation with role conflict (r = 0.226) and role overload (r = 0.234). Role conflict has a positive correlation with role overload (r = 0.646) and workplace harassment (r = 0.305). Workplace harassment does not have a significant correlation with role ambiguity while it has a positive correlation with role overload (r = 0.314).

Table 1. Correlation Analysis and Descriptive Statistics						
Variables	1	2	3	4	Mean	S.S.
Role Ambiguity (1)	1				2,52	0,703
Role Conflict (2)	,226**	1			3,35	0,732
Role Overload (3)	,234**	,646**	1		3,48	0,747
Work Harassment (4)	,007	,305**	,314**	1	0,64	0,645
**p≤0,05						

Mediation Analysis

The SPSS PROCESS macro 4 model was used to demonstrate the effects of role ambiguity and role conflict on workplace harassment and the intermediary role of role overload in this effect. The details of the analysis results seen in Figure 1 are presented in Table 2.
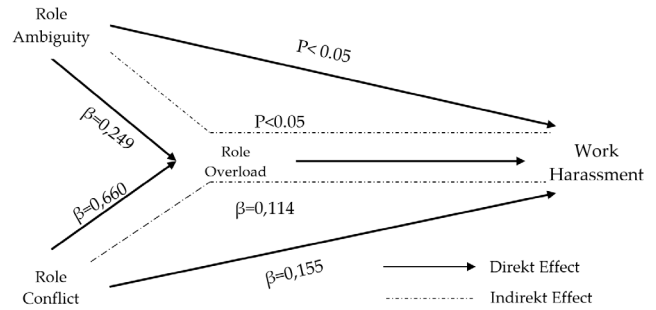
Figure 1: Research Model

According to the analysis results, role ambiguity has no direct or indirect effect on workplace harassment. On the other hand, role conflict affects workplace harassment directly (β= 0.155) and indirectly through role overload (β= 0.114). In line with these findings, the H1 hypothesis is rejected while the H2 hypothesis is accepted.

Table 2: Direct and Indirect Impact Table							
Variables	Direct Effect	Indirect Effect	Total Effect	LLCI	ULCI	t	p
Role Ambiguity	-	-	-	-	-	-	-
Role Conflict	0,155	0,114	0,269	0,166	0,372	5,148	0,000
Workplace harassment is the dependent variable.							

DISCUSSION

Low levels of role overload were found in certain studies conducted in Turkey (26) while in some studies it was found to be at moderate and high levels (27). High role overload of nurses is among the expected results. That is because fewer nurses need to take on more roles in order to meet the current and ever-increasing demand for health. The other expected outcome of the study was that nurses experienced more intense role conflict versus less role ambiguity. Similar studies have revealed findings that nurses experience more intense role conflict and less role ambiguity (27). This may be due to the fact that nurses know and perform the roles assigned to them well within the matrix organizational structure, but they have to perform more than one role at the same time under intense work pressure.

As a result of the study findings, role conflict and role ambiguity were found to have a positive correlation with role overload. There are similar studies in the literature (28).

Although not mediated by role overload, Ekici & Beder (29) found in their study that workload had a significant effect (38%) on predicting exposure to harassment at work, while Yildirim (4) found that 45% of nurses who faced harassment behavior were affected by workload.

The final finding of the study is that role overload does not play an intermediary role in workplace harassment caused by role ambiguity, but it has an enhancing role in workplace harassment caused by role conflict. Baillien & Witte (30) determined that the relationship between organizational change and bullying is precisely mediated by role conflict and job insecurity, while other stress factors have no mediating effects.

CONCLUSION

Nursing services play a very important role in providing effective, timely and efficient services without any interruptions in health systems. Research results confirm that nurses experience role conflict and role overload. Furthermore, role conflict and role overload experienced by nurses proved to have a positive correlation with their harassment at work. The results of the research reveal that nurses who experience workplace harassment in particular need to take precautions against increased role conflict and role overload. Executive nurses are primarily required to identify nurses who experience workplace harassment within the hospital and reduce their role overload as well as role conflicts they experience with their team-mates. Training nurses to cope with workplace harassment can be suggested as a possible precaution. Training may include necessary information about the possible effects of works carried out by nurses and ways of coping with workplace harassment. In addition, good communication and executive support between nurses and other health workers can reduce the negative incidents experienced by nurses such as role conflict and harassment at work. It is thought that participation of nurses in decision-making processes and the organizational structure can be increased if employees work as a team thanks to precautions and support networks

LIMITATIONS OF THE STUDY

The main limitation of the study is that it was carried out only in public hospitals in Sakarya, Turkey. In order to increase the generality of the study, it is recommended that the study be repeated with larger samples in public and private hospitals.

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How Does the COVID-19 Pandemic Affect Nursing Students' Career Choices? A Quantitative Study

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ABSTRACT

Aims: The purpose of this study investigated how the COVID-19 pandemic affected nursing students' career choices.

Methods: The study population consisted of 306 students from the Faculty of Nursing (n=234) and the Faculty of Health Sciences (n=72). The sample consisted of 227 students. Data were collected online using a descriptive characteristics questionnaire and the Nursing Career Decision Scale.

Results: Students had a mean Nursing Career Decision Scale score of 100.08. Students with working mothers had higher Nursing Career Decision Scale scores than those with non-working mothers. Being a first-time university students had higher Nursing Career Decision Scale scores than those who had being university before. Those who did not plan to change their nursing department had higher Nursing Career Decision Scale scores than those who thought about changing their department (p<.05). The pandemic affected students' career choices in general and encouraged them to pursue careers in nursing in particularly (p<.05).

Conclusion: In this study results showed that the variables of "faculty," "mother's employment status," "being a first-time university student," and "considering changing department of nursing" significantly affected students' Nursing Career Decision Scale scores (p<.05).

Keywords: COVID-19; career choice; nursing student

Covid-19 Pandemi Süreci, Hemşirelik Öğrencilerinde Meslek Seçimini Nasıl Etkiledi? Kantitatif Çalışma

ÖZET

Amaç: Bu çalışmanın amacı, COVID-19 pandemisinin hemşirelik öğrencilerinin kariyer seçimlerini nasıl etkilediğini araştırmaktır.

Yöntem: Araştırmanın evrenini Hemşirelik Fakültesi (n=234) ve Sağlık Bilimleri Fakültesi'nden (n=72) 306 öğrenci oluşturmuştur. Örneklem 227 öğrenciden oluşmaktadır. Veriler, tanımlayıcı özellikler anketi ve Hemşirelik Meslek Seçimi Ölçeği kullanılarak çevrimiçi olarak toplanmıştır.

Bulgular: Öğrencilerin ortalama Hemşirelik Meslek Seçimi Ölçeği puanı 100.08'di. Anneleri çalışan öğrencilerin, anneleri çalışmayanlara göre Hemşirelik Meslek Seçimi Ölçeği puanları daha yüksekti. İlk kez üniversiteye başlayan öğrencilerin daha önce üniversiteye başlayanlara göre Hemşirelik Meslek Seçimi Ölçeği puanları daha yüksekti. Hemşirelik bölümünü değiştirmeyi düşünmeyenlerin Hemşirelik Meslek Seçimi Ölçeği puanları, bölüm değiştirmeyi düşünenlere göre daha yüksekti (p<.05). Pandemi, genel olarak öğrencilerin meslek seçimlerini etkiledi ve onları hemşirelik alanında kariyer yapmaya teşvik etti (p<.05).

Sonuç: Bu çalışmanın sonuçları, "fakülte", "annenin çalışma durumu", "ilk kez üniversite öğrencisi olma" ve "hemşirelik bölümünü değiştirmeyi düşünme" değişkenlerinin, öğrencilerin Hemşirelik Meslek Seçimi Ölçeği puanlarını anlamlı olarak etkilediğini göstermiştir (p<.05).

Anahtar Kelimeler: COVID-19; kariyer seçimi; hemşirelik öğrencisi

Anovel coronavirus (nCoV-19) that emerged in Wuhan/China at the end of 2019 has been responsible for the current COVID-19 pandemic. It has been the most attention-getting event of 2020. Most, if not all countries, were caught unprepared by it. The virus spread rapidly, while administrations were having a tough time grasping the gravity of the situation. The World Health Organization (WHO) classified COVID-19 as a pandemic on March 11, 2020 (1). The pandemic has dramatically affected and continues to affect our lives medically, socially, professionally, politically, economically, mentally, physically, and educationally (2, 3).

Working actively during pandemics is a challenge in itself (4). The COVID-19 pandemic has reminded us that we urgently need to strengthen the global health workforce (1). Nurses make up the largest workforce in healthcare and are on the frontline of patient care in times of crisis (5). As put by Dr. Tedros Adhanom Ghebreyesus, WHO Director-General, "Nurses are the backbone of any health system. Today, many nurses find themselves on the frontline in the battle against COVID-19" (5). What is more, WHO declared 2020 as the "International Year of the Nurse and the Midwife," highlighting the significance of the profession during the pandemic (6).

Nurses are responsible for caring for patients on a day-to-day basis. Students who would like to pursue careers in nursing are expected to be interested and enthusiastic about the profession and make informed decisions based on the facts and future of the profession and the healthcare system (7, 8). People devote about one-third of their lives to their jobs. Career choice is a critical aspect of life because it may open up new doors of opportunity or wedge them more firmly shut. Career choice is a complex process because it is affected by various factors. Choosing a career also means choosing a lifestyle and standards of living (9-11). Studies before the pandemic categorized the factors affecting nursing students' choice of the profession into four: internal, external, sociodemographic/economic, and interpersonal. Internal factors are willingness to help others and a particular interest in healthcare. External factors are a successful career, professional reputation, and autonomy. Sociodemographic/economic factors are gender, financial rewards, and job security. Interpersonal factors are influences of family and professional members (7, 12-14).

Outbreaks are global health crises that have led to administrative and lifestyle changes throughout history. Outbreaks profoundly affect all aspects of life, including economy, politics, education, mental health, etc. (2). The success of preventive measures depends on the cooperation among all parties involved (citizens, healthcare workers, and institutions). All healthcare professionals have been working tirelessly since the onset of the pandemic (15). Nurses provide hands-on care and treatment for both COVID-19 patients and other patients. They are more likely to contract the virus because they are exposed to it as they care for those in need (16). According to the International Council of Nurses (October 20, 2020), more than 1,500 nurses in 44 countries and more than 20,000 healthcare workers worldwide died from COVID-19 (17). By the nature of their profession, nurses are aware of the risk of infection and worried about infecting their families (18).

Outbreaks enable us to better understand the skills that are fundamental to health (19). The pandemic has changed people's habits, priorities, expectations, and perspectives in its entirety. Healthcare professionals, especially nurses, who are in close contact with patients in high-risk settings during the pandemic may have second thoughts about their career choices. The global fight against the pandemic has reminded us all of the importance of health-related professions. Therefore, it is important to determine the impact of the pandemic on career choices. Although earlier studies have looked into the factors affecting nurses' career choices, no research has investigated the impact of the pandemic on nurses' career choices. Therefore, this study focused on in what way the pandemic affected nursing students' career choices. The purpose of this study was to investigate the impact of the pandemic on nursing students' career choices. This study was concerned with answering the following research questions:

Research question 1: What factors encourage students to pursue careers in nursing?

Research question 2: How does the COVID-19 pandemic affect nursing students' career choices?

METHODS

Study Design and Sample
This descriptive research was conducted in the 2020-2021 academic year. The study population consisted of 306 first-year students from the Faculty of Nursing (n=234) and the Faculty of Health Sciences (n=72) of a university south of Turkey. No sampling was performed. All volunteers were included in the sample (n=227; 74.18%).

Data Collection
The data were collected online (Google forms) using a descriptive characteristics questionnaire and the Nursing Career Decision Scale between 15 and 29 October 2020. The researchers informed all students of the purpose, procedure, and confidentiality of the study. All students read

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an e-consent form, and those who volunteered gave informed consent before they filled out the forms.

Data Collection Tools

The Descriptive Characteristics Questionnaire: The descriptive characteristics questionnaire was based on a literature review conducted by the researchers. It consisted of 16 items on faculty, age, gender, parents' education, employment, and income status, participant's conscious choice of university and department, considering changing department of nursing, having tested positive for COVID-19, knowing someone who had tested positive for COVID-19, and the effect of the pandemic on career choices in general and choosing the nursing profession in particular (20-22).

The Nursing Career Decision Scale (NCDS): Scale was developed by Zysberg and Berry to determine the factors affecting students' career choices (23). The scale was adapted to Turkish by Önler and Saraçoğlu (24). It consists of 17 items and two subscales: vocational congruency (11 items) and survival (six items). The items are scored on a Likert-type scale converted into a 0-100 score, with a higher score indicating a higher effect on career choice. The total score and subscale scores are the sum score divided by the number of items. The scale is not a diagnostic measure, and the score range does not signify anything. The total scale and the subscales "vocational congruency" and "survival" have a Cronbach's alpha of 0.77, 0.63, and 0.79, respectively. The total scale had a Cronbach's alpha of 0.77 in this study.

Data Analysis

The data were analyzed using Statistical Analysis Software (SAS) and R at a significance level of .05 and a confidence interval of 95%. The descriptive data were analyzed using number, percentage, mean, and standard deviation. Cronbach's alpha coefficient was calculated to determine the internal consistency of the NCDS. Skewness and kurtosis coefficients were used for normality testing. The mean and median values were similar, and the skewness and kurtosis coefficients ranged from -1.5 to +1.5, indicating that the data were normally distributed (Figure 1). A multivariate analysis of variance (MANOVA) was used to reduce Type I error. An Analysis of Covariance (ANCOVA) was used to determine the effect of covariates. Box's test for equivalence of covariance matrices yielded p>0.05, suggesting the equality of the group covariance matrices. Therefore, Wilks's lambda distribution was used for test statistics.

RESULTS

Demographic Characteristics

Of participants, 179 (78.9%) were the students of the Faculty of Nursing, 162 (71.4%) were women, 97 (42.7%) had mothers with a primary school degree, 89 (39.2%) had fathers with a primary school degree, 200 (88.1%) had non-working mothers, and 149 (65.6%) had working fathers. One hundred and three families (45.4%) had a monthly income of 2000-3999 TL. Ninety-six participants (42.3%) lived in the city center. The majority of the participants (n=205, 90.3%) were first-time university students. More than half the participants (n=132; 58.1%) listed nursing department as their first, second, third, or fourth choice. More than half the participants (n=146; 64.3%) did not considering changing department of nursing. The majority of the participants (n=206; 90.7%) had never tested positive for COVID-19. However, more than half the participants (n=136; 59%) knew someone (a family member, friend, acquaintance, neighbor, etc.) who had tested positive for COVID-19. More than half the participants (n=129; 56.8%) stated that the pandemic did not affect their career choices in general. One hundred and twenty-three participants (54.2%) stated that the pandemic did not affect their career choice in nursing in particular (Table 1).

Nursing Career Choice

After the outliers were removed, participants had a total NCDS score of 100.08±23.66 (Min= 25; Max=151). They had a mean "vocational congruency" and "survival" subscale score of 69.85±21.62 (Min= 0; Max=110) and 30.23±9.02 (Min= 3; Max=51), respectively (Table 2).

Multivariate Analysis of Variance for NCDS Total Mean Scores

Box's test for equivalence of covariance matrices yielded p>0.05, suggesting the equality of the group covariance matrices. Therefore, Wilks's lambda distribution was used for test statistics. The results showed that the variables of "faculty," "mother's employment status," "being a first-time university student," and "considering changing department of nursing" significantly affected participants' NCDS scores (p<.05). In other words, participants from the faculty of nursing had higher NCDS scores than those from the faculty of health sciences (p<.045). Participants with working mothers had higher NCDS scores than those with non-working mothers (p<.024). The first-time university students had higher NCDS scores than second bachelor's degree students (p<.015). Participants who considered changing department of nursing had higher NCDS scores than those who did not considering changing department of nursing (p<.000). The pandemic affected participants' career choices in general and encouraged them to pursue careers in nursing in particular (Table 3).

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Table 1: Demographic Characteristics and Career Choice (n=227)			
Demographic Characteristics	**Mean±SD**		
Age	18.98 ± 1.05		
		N	%
Faculty	Faculty of nursing	179	78.9
	Faculty of health sciences	48	21.1
Gender	Woman	162	71.4
	Man	65	28.6
Mother's education (degree)	Illiterate	37	16.3
	Literate	22	9.7
	Primary school	97	42.7
	Secondary school	31	13.7
	High school	31	13.7
	Bachelor's or higher	9	4.0
Father's education (degree)	Illiterate	5	2.2
	Literate	18	7.9
	Primary school	89	39.2
	Secondary school	42	18.5
	High school	45	19.8
	Bachelor's or higher	28	12.3
Mother's employment status	Employed	28	11.9
	Unemployed	200	88.1
Father's employment status	Employed	149	65.6
	Unemployed	78	34.4
Monthly family income (TL)	Less than 2000	75	33.0
	2000-3999	103	45.4
	4000-5999 TL or more	49	21.6
Place of residence	City center	96	42.3
	District	77	33.9
	Town/village	54	23.8
Earlier college experience	First time	205	90.3
	Second time (internal/external transfer)	22	9.7
Nursing department preference order	1-4th	132	58.1
	5-8th	32	14.1
	9-12th	24	10.6
	13-16th	17	7.5
	17-20th or higher	22	9.7
Considering changing department of nursing	Yes	81	35.7
	No	146	64.3
Having tested positive for COVID-19	Yes	21	9.3
	No	206	90.7
Knowing someone (family member, friend, acquaintance, neighbor, etc.) who had tested positive for COVID-19	Yes	136	59.9
	No	91	40.1
The impact of the COVID-19 pandemic on career choice	Positive	43	18.9
	Negative	18	7.9
	Undecided	37	16.3
	None	129	56.8

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The impact of the COVID-19 pandemic on choosing the nursing profession	Positive	43	18.9
	Negative	22	9.7
	Undecided	39	17.2
	None	123	54.2
Note.SD=Standard Deviation; TL=Turkish lira			

Table 2: NCDS Total and Subscale Scores (n=227)		
Nursing Career Decision Scale and subscales	**Mean ± SD**	**Min-Max**
Vocational congruency (0-110)	69.85 ± 21.62	0-110
Survival (0-60)	30.23 ± 9.02	3-51
Total (0-170)	100.08 ± 23.66	25-151
Note. SD=Standard Deviation; NCDS= Nursing Career Decision Scale		

Table 3: Multivariate Tests for NCDS Total Score (n=227)		
Demographic Characteristics	**F**	**p**
Age	.724	.630
Faculty	4.111	.045*
Gender	.714	.400
Mother's education (degree)	.519	.762
Father's education (degree)	.759	.581
Mother's employment status	5.181	.024*
Father's employment status	.958	.329
Monthly family income (TL)	1.222	.297
Place of residence	.743	.477
Family type	.309	.579
Earlier college experience	6.364	.015*
Considering changing department of nursing	27.691	.000*
Note. NCDS= Nursing Career Decision Scale η²=.316 Observed Power= .702 Degree of Freedom= 22 *p < .05		

Figure 1: Normally distributed

DISCUSSION

Since the onset of the pandemic, people on social media platforms and TV channels have talked about how vital nursing is and why the world needs more nurses than ever (25). Multiple newspapers have also covered how the pandemic has affected students' choice of department (26). These positive developments make nursing more visible and attractive. Research also shows that students are more interested in nursing and use social and traditional media platforms to learn more about it (13, 27). This paper investigated how the pandemic affected nursing students' career choices. Participants had quite high total NCDS and "vocational congruency" subscale scores. We think that this is because nurses have been among the most sought-after employees since the onset of the pandemic and will continue to be so in the near future, and students know it too. Participants' mean "survival" subscale score was the same as their total mean NCDS score. On the contrary, earlier studies have reported low total NCDS and "vocational congruency" subscale scores (10, 21). Therefore, our results point to the positive effect of the pandemic on students' career choices. Our participants had twice as high "vocational congruency" score as "survival" score, suggesting that students who choose to pursue careers in nursing consider themselves fit for the profession.

Covariance analysis for NCDS total score and some variables
This study also investigated whether the covariates of "having tested positive for COVID-19" and "knowing someone (a family member, friend, acquaintance, neighbor, etc.) who had tested positive for COVID-19" affected participants' career choices. Although most participants stated that the pandemic had no impact on their career choices in general and their choice of the nursing profession in particular (Table 1), those who stated the otherwise caused a significant difference in NCDS scores. The covariance analysis results showed that the pandemic affected participants' career choices in general (p<.027) and encouraged them to pursue careers in nursing in particular ((p<.039) (Table 4).
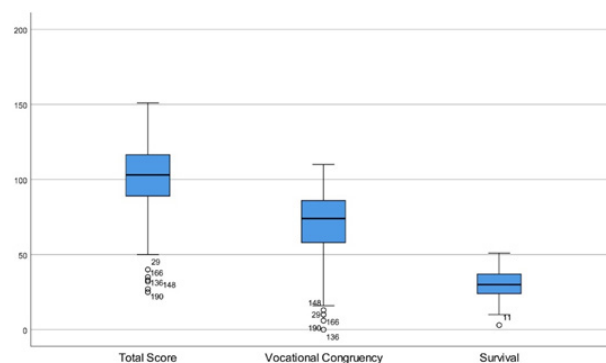
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Table 4: Covariance Tests for NCDS Total Score and Variables (n=227)				
Variables	**Status**	**Mean**[a]	**F**	**p**
The impact of the COVID-19 pandemic on choosing the nursing profession	Positive	105.314	1.824	.039*
	Negative	94.432		
	Undecided	98.410		
	None	98.957		
The impact of the COVID-19 pandemic on career choice	Positive	114.653	1.940	.027*
	Negative	97.908		
	Undecided	94.706		
	None	96.019		
Note. NCDS= Nursing Career Decision Scale a. Covariates in the model are evaluated at the following values: Having tested positive for COVID-19 = 1.9075, knowing someone (family member, friend, acquaintance, neighbor, etc.) who had tested positive for COVID-19 = 1.4009. *p < .05				

Our results showed that the variables of "faculty," "mother's employment status," "being a first-time university student," and "considering changing department of nursing" significantly affected participants' NCDS mean scores. In other words, participants from the faculty of nursing had higher NCDS mean scores than those from the faculty of health sciences. This may be because the faculty of nursing is in the city center and is harder to get into than the faculty of health sciences. However, some researchers reported that the place of residence did not affect NCDS scores (28). Based on our result, we can state that the students of the faculty of nursing higher awareness and readiness concerning career choice.

There was no significant difference in NCDS scores between participants with and without working fathers. However, their scores differed by mothers' employment status. Participants with working mothers had higher NCDS scores than those with non-working mothers. This may be because working mothers who are more involved in homeschooling are more likely to influence their children's career decisions and encourage them to get into nursing school. Ogunyewo et al. also found that working parents influenced their children's career decisions more than non-working parents did (13). However, some studies found no difference in NCDS scores between students with and without working parents (28, 29).

Participants admitted to university during the pandemic had higher "vocational congruency" subscale scores than those who had had university experience before and decided to study nursing as their second degree. We think that first-time university students had the opportunity to learn more about the nursing profession during the pandemic,

and therefore, explored more career options and made more informed decisions about the university they wanted to go to and the department they wanted to study.

Participants who considered changing department of nursing had significantly higher NCDS scores than those who did not considering changing department of nursing. More than half the participants listed nursing as their top choice department. We can state that the students who get into nursing during the pandemic choose the profession willingly and are content with it and determined to practice it. Our result is consistent with the literature (7, 9, 14, 20, 21, 28).

The pandemic is believed to affect first-year students' career choices because of the rising demand for healthcare services and healthcare workers since its onset. The image of the nursing profession has become a valued career choice for people. Although most participants stated that the pandemic had no impact on their career choices in general and their choice of the nursing profession in particular, those who stated the otherwise caused a significant difference in NCDS scores. In other words, the pandemic has positively affected the participants' career choices in general and encouraged them to pursue careers in nursing in particular. Having tested positive for COVID-19 or knowing someone (a family member, friend, acquaintance, neighbor, etc.) who had tested positive for COVID-19 might also have contributed to the difference in NCDS scores. Cerit et al. found that nursing students with positive attitudes towards the profession had higher "vocational congruency" scores than those with negative attitudes (30). Studies before the pandemic reported lower NCDS scores than what we found (21, 31). This difference can be

accounted for by the pandemic, which has improved the image of the nursing profession worldwide.

CONCLUSION

The pandemic is still growing, and possible mutations are a constant threat to global health. Although there is no going back to "old normal," universities have to continue their academic programs. The pandemic has dealt a blow to most professions, but one of its unexpected benefits has been the global recognition of the nursing profession. It has also affected first-year students' career choices in general and encouraged them to pursue careers in nursing in particular. Students who willingly choose the nursing profession are likely to provide better care and pay much more attention to public health in the future. The increased demand for nurses worldwide shows that the profession is finally getting the recognition that it deserves.

LIMITATIONS

This study is limited to the study findings of nursing students from two faculties. The results are sample-specific, and therefore, cannot be generalized to the whole population. However, this is the first study to look into the impact of the pandemic on nursing students' career choices. Therefore, further research with a larger sample is recommended to learn more about the subject.

DECLARATIONS

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Decision Number: 823, Date:21.10.2020).

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GAS, RDI and EK. The first draft of the manuscript was written by GAS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

The Effects of Peer Relationships on Smartphone Addiction among Adolescents

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ABSTRACT

Purpose: The aim of this study is to determine the effect of peer relationships on smartphone addiction among adolescents.

Methods: Population of this cross-sectional study was composed of students in the high schools of the Directorate of National Education in the city center of Batman province. The sample consisted of three high schools (3000 students) which were selected from the Provincial Directorate for National Education by using the method of drawing lots. The sample size was calculated as 707 students based on the power analysis. "Introductory Information Form", "Peer Relationship Scale", and "Smartphone Addiction Scale" were utilized to gather data between May 2018 and June 2018. Percentage distribution, mean, independent samples t-test, analysis of variance, Kruskal-Wallis test and regression analysis were employed to assess the data.

Results: The participants' total mean scores were 45.61±11.93 in Peer Relationship Scale and 28.93±12.61 in Smartphone Addiction Scale. Peer relationships of the adolescents influenced their smartphone addiction at the rate of 38% (p 0.05).

Conclusion: It was concluded that the adolescents had moderate level of peer relationships and smartphone addictions. Their peer relationships affected their smartphone addition. In the study, it is recommended for psychiatric nurses to inform the students and organize trainings in order to increase the peer relationships of adolescents and decrease their smartphone addiction.

Keywords: Addiction; Adolescents; Peer Relationships; Smartphone

Ergenlerin Akran İlişkilerinin Akilli Telefon Bağımlılığına Etkisi

ÖZET

Amaç: Bu araştırmanın amacı, ergenlerin akran ilişkilerinin akıllı telefon bağımlılığına etkisini belirlemektir.

Yöntem: Kesitsel çalışmanın evrenini Batman il merkezinde Milli Eğitim Müdürlüğü'ne bağlı liselerde okuyan öğrenciler oluşturmaktadır. Araştırmanın örneklemi için İl Milli Eğitim Müdürlüğünden öğrenci yoğunluğuna göre kura çekme yöntemi kullanılarak üç lise (3000 öğrenci) seçilmiştir. Araştırmanın örneklemi güç analizi ile 707 öğrenci olarak belirlenmiştir. Araştırmada "Tanıtıcı Bilgi Formu", "Akran İlişkileri Ölçeği" ve "Akıllı Telefon Bağımlılığı Ölçeği" kullanılmıştır. Veriler Mayıs 2018 ile Haziran 2018 arasında toplanmıştır. Verilerin değerlendirilmesinde yüzde dağılım, ortalama, bağımsız örneklemler t-testi, varyans analizi, Kruskal-Wallis ve regresyon analizi kullanılmıştır.

Bulgular: Araştırmada ergenlerin akran ilişkileri toplam puan ortalamasının 45.61 ± 11.93 ve akıllı telefon bağımlılığı toplam puan ortalamalarının 28.93±12.61 olduğu belirlenmiştir. Araştırmada ergenlerin akran ilişkilerinin akıllı telefon bağımlılığını % 38 oranında etkilediği bulunmuştur (p<0.05).

Sonuç: Araştırmada ergenlerin akran ilişkileri ve akıllı telefon bağımlılığının orta düzeyde olduğu saptanmıştır. Ergenlerin akran ilişkilerinin akıllı telefon bağımlılığını etkilediği tespit edilmiştir. Araştırmada ergenlerin akran ilişkilerini arttırmak ve akıllı telefon bağımlılıklarını azaltmak için psikiyatri hemşireleri tarafından öğrencilerin bilgilendirilmesi ve eğitimler düzenlenmesi önerilmektedir.

Anahtar Kelimeler: Akıllı telefon; Akran İlişkileri; Ergenler; Bağımlılık

Today's world is rapidly developing, thus leading to many new problems. These problems affect people of all age groups, resulting them in encountering new ones (1,2). Especially the adolescents among the age groups undergo a very rapid change and transformation and are more affected by these new problems (2). Adolescence period is a period in which individuals undergo social, emotional, developmental and mental changes very rapidly (1).

One of the technological tools that negatively affect the adolescents is undoubtedly mobile phones (3). Adolescents use smartphones for most of their lives on these days. The number of users has increased considerably in recent years in Turkey especially in terms of smartphone sales figures (2,3). A previous study reported that adolescents possessed a mobile phone by 76% and also 40% of them had a second mobile phone (2).

It can be asserted that the use of smartphone in world and in Turkey has gone beyond its basic function, instead has turned addiction that causes various physical and mental disorders (3). Kim (4) found that smartphone addiction led to serious abuse problems in young students It can be asserted that the smartphone addiction plays a major role in peer relationships since it consumes much of the adolescents' time.

Adolescents often spent most of their time with their peers at or outside the school and have the tendency to exhibit common behaviors with their peers (5). During the adolescence period, young people tend towards friend groups rather than their families. Being popular among friends and being liked and accepted by them are considered as an important condition of self-esteem of adolescents (4,5). Therefore, peer relationships become more prominent and important in adolescence. Changes occur in terms of social context and social norms in the period from childhood to adolescence, which thus also increase the importance of peers (5,6). Adolescents begin to spend more time with their peers, act autonomously from their parents and thus spend more time with their peers (7,8).

Effective use of the Internet can positively help adolescents improve their relationships with friends. However, uncontrolled use and overuse of the internet can also lead them to feel lonely and isolated by preventing them from socializing (9). Young and Case (10) determined in their study that adolescents who used the internet too much had poorer relationships with their families and peers.

The number of the related studies is limited. We think that the results of the current study would make contribution to the practices in the psychiatric nursing field and identify the problems experienced by adolescents. This study is aimed to determine the effect of peer relationships on smartphone addiction among the adolescents.

METHOD

Type of the Study
The present study was conducted with cross-sectional design to evaluate the effect of peer relationships of the adolescents on their smartphone addiction.

Study Place and Time
The study was conducted with the students studying in three high schools affiliated to Batman Provincial Directorate of National Education between May and November 2018.

Population and Sample
The population consisted of the students (42.000 students) studying in 41 high schools within the body of Provincial Directorate of National Education in the city center of Batman province. The sample consisted of students (3000 students) studying in three high schools which were selected from the population by drawing lots. The sample size was calculated to be 707 based on power analysis at significance level of 0.05, confidence interval of 0.95, effect size of 0.3 and the power to represent the population of 0.95. School numbers of the students were listed and then selected based on simple random sampling method.

Inclusion Criteria
- Being aged between 13-18 years
- Being open to communication

Exclusion Criteria
- Having no mental or physical problem preventing communication.

Data Collection Tools

Introductory Information Form

Introductory Information Form has 8 questions about socio-demographic characteristics of the students (age, gender, mother's educational level and profession,

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father's educational level and profession, income level, grade level).

Peer Relationship Scale (PRS)

Kaner (2002) developed PRS based on Social Control and Social Learning Theories to investigate peer relationships (11). Its Cronbach's alpha coefficient was determined as 0.93. PRS has 18 items and 4 subscales; Commitment (1,4,10,11,12,13,15,16), Confidence and Identification (2,8,9,18), Self-Disclosure (6,7,14), and Loyalty (3,5,17) subscales. Its items are rated between 1 (always) and 5 (never) points. Total score ranges between 1 and 90. High scores signify adolescents' perceptions of positive relationships with their peers. In this study, its Cronbach's alpha coefficient was determined as .89.

Smartphone Addiction Scale Short Version (SAS)

SAS is a self-report scale developed by Kwon et al. (12). based on Young's items on the internet addiction and the future of smartphones. Demirci et al., adapted the scale into Turkish (13). In 2015, Noyan et al., conducted Turkish validity and reliability study of its short version (3). The Cronbach's alpha coefficient of the scale is 0.92. It has 10 items rated with 6-point Likert type ranging between 1 (strongly disagree) and 6 (strongly agree). It has a single factor and no subscales. Total score ranges between 10 and 60. High scores signify a high risk of smartphone addiction. In this study, its Cronbach's alpha coefficient was determined as .90.

Data Collection

The data were gathered from three high schools within the body of Batman Provincial Directorate of National Education between May 2018 and June 2018. "Introductory Information Form", PRS, and SAS were employed to collect data. The first researcher applied the data collection forms to students studying in these schools in their classrooms at the times deemed appropriate by the school administration. It took averagely 15-20 minutes for the students to complete these forms. Incomprehensible questions explained to students without any interpretation.

Data Analysis

The data were analyzed by utilizing SPSS 21.0 packaged software. Percentage for comparing descriptive characteristics of the adolescents, mean for calculating their scale mean scores, independent samples t test for comparing their scale mean scores with age groups and gender,

analysis of variance for comparing their scale mean scores with the grade level, father's educational level, mother's profession, father's profession, and income level, Kruskal-Wallis test for comparing their scale mean scores with mother's educational level, post-hoc test for determining which group causing the difference and regression analysis for determining how the scales affected each other were used in the data assessment. In the study, $p<0.05$ was accepted as significant.

Ethical Considerations

Approval from Inonu University Health Sciences Scientific Research and Publication Ethics Committee (APPROV NO: 2018/9-8 and legal permission was obtained from the institution on 09.11.2017. In the study, the high school students were under 18 years of age; therefore, they and their parents were informed about the purpose of the study and the opportunity of withdrawing the study at any time and their written and verbal consents were obtained.

This study was carried out based on the Principles of the Declaration of Helsinki.

Limitations

- The study is limited to students randomly selected from high school students in a city center located in the Southeastern Turkey.

- The adolescents aged between 13-19 years who were attending institutions in the study.

RESULTS

It was determined that 69% of the participants were aged between 16-18 years, 30.8% were twelfth graders, and 70.6% were female. The mothers of 39.6% of the adolescents were primary school graduates, the fathers of 29.9% were secondary school graduates, their mothers were unemployed 91.9%, their fathers were self-employed at the rate of 47.1%, and 84.9% of the adolescents had a good income status (Table 1).

It was found that the mean scores of the adolescents were 15.62±5.84 for the commitment subscale, 10.41±4.19 for the subscale of confidence and identification, 9.04±3.18 for the subscale of self-disclosure, and 10.52±3.14 for the subscale of loyalty and their total mean score was 45.61±11.93 for the peer relationship scale. PRS total mean score of the adolescents was moderate. Their SAS total mean score was 28.93±12.61. This score was moderate (Table 2).

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Table 1. Distribution of the Adolescents in terms of their Descriptive Characteristics (n=707)		
Descriptive Characteristics	**n**	**%**
Age Groups		
13-15	219	31
16-18	488	69
Grade		
9	160	22.6
10	141	19.9
11	188	26.6
12	218	30.8
Gender		
Male	208	29.4
Female	499	70.6
Mother's Educational Level		
Illiterate	188	26.6
Primary School	280	39.6
Secondary School	121	17.1
High School	99	14.0
Associate-Bachelor's Degree	10	1.4
Master's degree and higher	9	1.3
Father's Educational Level		
Illiterate	57	8.1
Primary School	171	24.2
Secondary School	207	29.3
High School	164	23.2
Associate-Bachelor's Degree	76	10.7
Master's degree and higher	32	4.5
Mother's Profession		
Unemployed	650	91.9
Civil servant	23	3.3
Worker	12	1.7
Self-employed	22	3.1
Father's Profession		
Unemployed	93	13.2
Civil servant	139	19.7
Worker	142	20.1
Self- employed	333	47.1
Income Status		
Very good	28	4.0
Good	600	84.9
Bad	60	8.5
Very Bad	19	2.7
TOTAL	**707**	**100.0**

Table 2. Total Mean Scores of Peer Relationship Scale and Smartphone Addiction Scale		
Scale	**Min-Max Point**	**Mean.±SD**
Addiction	8-38	15.62±5.84
Confidence and Identification	4-50	10.41±4.19
Self-Disclosure	3-15	9.04±3.18
Loyalty	3-17	10.52±3.14
Peer Relationships Total Score	18-120	45.61±11.93
Smartphone Addiction Total Score	10-60	28.93±12.61

PRS total score and loyalty and self-disclosure subscales total mean scores of the participants in terms of their age groups were statistically significant ($p<0.05$). The difference between the groups was associated with the age groups of 13-15 years. The difference between the grade level and total mean scores of commitment, self-disclosure, loyalty subscales and overall PRS was statistically significant ($p<0.05$). The advanced analysis revealed that the difference between the groups was associated with the tenth-graders. A significant correlation was found between the gender variable and self-opening and loyalty subscales of PRS ($p<0.05$). The difference between the groups was caused by female students. There was a statistically significant difference between the mother's educational level and commitment, self-disclosure, and loyalty subscales of PRS and its total mean score ($p<0.05$). The advanced analysis revealed that the difference between the groups was caused by the post graduate and higher educational level. The difference between the father's educational level and commitment, confidence and identification and self-disclosure subscales of PRS was statistically significant ($p<0.05$). The advanced analysis revealed that the reason for the difference between the groups was the post graduate and higher educational level. A significant correlation was found between the mother's profession and total scores of confidence and identification subscales and PRS ($p<0.05$). The advanced analysis revealed that the reason for the difference between the groups was the unemployed mothers. There was a statistically significant correlation between the father's profession variable and confidence and identification subscales of PRS ($p<0.05$). The advanced analysis revealed that the reason for the difference between the groups was the unemployed fathers. A significant correlation was found between the variable of income level and commitment, self-disclosure, confidence and identification and loyalty subscales and PRS total score ($p<0.05$). The advanced analysis revealed that the difference between the groups was caused by those with very high income level.

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Table 3. Comparison of Peer Relationships Scale Subscale Total Mean scores and Smartphone Addiction Scale Total Mean scores of the Adolescents in terms of their Socio-Demographic Characteristics								
Sociodemographic Characteristics				Commitment	Confidence and Identification	Self-disclosure	Loyalty	Peer Relationships Total Score	Smartphone Addiction Total Score
		n	%						
Age Groups	13-15	219	31.0	15.85±5.94	10.76±3.86	9.79±3.24	10.88±3.16	47.30±12.09	28.43±12.41
	16-18	488	69.0	15.52±5.80	10.25±4.33	8.71±3.10	10.36±3.12	44.85±11.79	29.16±12.71
	Test Value Significance			t=0.710 p=0.482	t=1.496 p=0.135	t=4.250 **p=0.000**	t=2.028 **p=0.043**	t=0.-715 **p=0.002**	t=0.-713 p=0.476
Grade Level	9	160	22.6	15.36±5.34	10.50±3.58	9.80±3.33	10.80±3.36	46.46±11.90	27.04±11.36
	10	141	19.9	16.02±5.75	10.97±4.11	9.41±2.99	11.10±3.16	47.52±11.93	27.40±12.30
	11	188	26.6	14.54±5.34	10.40±4.69	9.09±3.15	10.29±3.09	44.34±11.76	30.23±13.97
	12	218	30.8	16.49±6.51	9.97±4.19	8.21±3.05	10.15±2.93	44.83±11.96	30.20±12.25
	Test Value Significance			F=3.357 **p=0.019**	F=2.025 p=0.109	F=9.183 **p=0.000**	F=3.398 **p=0.018**	F=4.247 **p=0.005**	F=3.324 **p=0.019**
Gender	Male	208	29.4	15.43±5.39	10.02±4.74	9.48±3.06	9.84±3.51	44.78±11.75	29.72±12.85
	Female	499	70.6	15.70±6.02	10.57±3.94	8.86±3.22	10.81±2.92	45.95±11.99	28.61±12.51
	Test Value Significance			t=0.-551 p=0.582	t=-1.580 p=0.115	t=2.339 **p=0.020**	t=-3.766 **p=0.000**	t=-1.279 p=0.201	t=1.070 p=0.285
Mother's Educational Level	Illiterate	188	26.6	15.40±5.85	10.05±3.60	9.16±3.23	10.37±3.33	45.00±11.90	26.31±12.93
	Primary School	280	39.6	16.75±6.29	10.81±4.70	9.38 ±2.88	10.73±3.17	47.68±12.57	28.06±11.52
	Secondary School	121	17.1	15.39±5.39	10.54±4.02	8.42±3.60	10.36±2.96	44.72±11.08	31.66±12.08
	High School	99	14.0	13.19±4.10	9.74±3.89	8.86±3.25	10.88±261	42.69±10.13	31.46±14.11
	Higher education	10	1.4	17.00±6.42	10.40±5.42	7.90±2.64	9.50±3.02	44.80±13.98	34.70±12.64
	and more	9	1.3	13.55 ±4.44	10.77±2.22	7.66±3.96	6.77±3.34	38.77±9.05	40.22±11.57
	Test Value Significance			KW=6.142 **p=0.000**	KW=1.164 p=0.325	KW=2.312 **p=0.043**	KW=3.491 **p=0.004**	F=2.976 **p=0.011**	KW=20.889 **p=0.000**
Father's Educational Level	Illiterate	57	8.1	17.01±5.58	11.78±3.93	10.35±68	10.59 ±2.73	49.75±9.90	26.78±10.30
	Primary School	171	24.2	15.60±6.23	10.45±4.05	8.93±3.31	10.70±3.57	45.69±12.84	28.05±12.80
	Secondary School	207	29.3	15.97±5.54	10.39±3.65	8.95±2.90	10.52±3.10	45.84±11.06	27.80±12.50
	High School	164	23.2	16.15±6.25	9.78±4.26	9.12±3.24	10.32±2.96	45.38±13.21	30.76±13.05
	Higher education	76	10.7	13.56±4.83	10.94±5.91	8.46±3.60	10.85±2.58	43.82±10.98	28.85±12.41
	and more	32	4.5	13.21±4.57	9.78±2.75	8.93±3.31	9.78±3.72	41.71±9.04	35.68±11.84
	Test Value Significance			F=4.116 **p=0.001**	F=2.421 **p=0.034**	F=2.554 **p=0.027**	F=0.767 p=0.574	F=2.056 **p=0.068**	KW=6.298 **p=0.005**
Mother's Profession	Unemployed	650	91.9	15.58±5.97	10.30±4.19	9.02±3.22	10.47±3.17	52.38±12.10	29.09±12.71
	Civil servant	23	3.3	16.52±3.65	13.82±4.04	10.04±2.61	11.69±2.42	45.08±7.92	31.86±10.30
	Worker	12	1.7	13.16±1.99	9.33±1.61	7.41±1.92	9.25±2.63	39.16±4.46	22.75±14.17
	Self-employed	22	3.1	17.09±4.70	10.63±4.04	9.68±2.81	11.59±2.44	49.00±9.90	24.59±9.52
	Test Value Significance			F=1.241 p=0.294	F=5.702 **p=0.001**	F=1.740 p=0.158	F=2.261 p=0.080	F=3.977 **p=0.008**	KW=8.189 p=0.077

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Father's Profession	Unemployed	93	13.2	16.34±6.75	11.92±4.42	8.91±3.95	10.41±0.25	47.60±14.03	29.89±13.93
	Civil servant	139	19.7	14.75±5.12	9.69±3.14	9.02±3.14	10.38±2.77	43.85±9.00	29.12±11.79
	Worker	142	20.1	15.38±5.69	10.10±5.38	8.73±2.91	10.88±3.31	45.10±12.63	32.04±13.50
	Self-employed	333	47.1	15.89±5.90	10.41±3.84	9.22±3.07	10.46±3.18	46.00±11.99	27.27±11.93
	Test Value Significance			F=1.675 p=0.171	F=7.384 **p=0.000**	F=0.887 p=0.447	F=0.851 p=0.466	F=1.481 p=0.219	F=5.078 **p=0.002**
Income status	Very high	28	4.0	12.35±4.00	10.60 ±3.72	7.10±3.14	8.53±3.56	38.60±9.38	32.10±13.28
	High	600	84.9	15.72±5.91	10.26±4.23	9.01±3.16	10.51±3.09	45.51±12.06	28.95±12.68
	Low	60	8.5	16.30±5.98	11.15±3.89	10.01±2.90	10.93±3.28	48.40±11.30	27.28±12.14
	Very low	19	2.7	15.31±3.98	12.36±4.07	9.89±3.60	12.57±1.46	50.15±48.06	28.89±10.80
	Test Value Significance			F=3.283 **p=0.020**	F=2.843 **p=0.037**	F= 5.903 **p=0.001**	F=6.962 **p=0.000**	F=6.614 **p=0.000**	KW=2.883 p=0.424

When the socio-demographic characteristics and smartphone addiction scale total mean scores of the adolescents were compared, a statistically significant difference was found between SAS total mean score and grade, mother's educational level, father's educational level, and father's profession (p<0.05, Table 3). The advanced analysis revealed that the reason for the difference between the groups in terms of the grade level was the tenth-graders. Also the difference in terms of the educational levels of the mother and father was associated with the post graduate and higher educational level.

In the study, peer relationships of the adolescents were statistically significant in explaining smartphone addiction (p<0.05). Their peer relationships accounted for their smartphone addiction at the rate of 38% (Table 4).

DISCUSSION

The findings of the present study indicated that the adolescents had moderate level of peer relationships. In their study, Argon and Yılmaz (9) reported that peer relationships of the adolescents studying at high school were at moderate level. The moderate peer relationships of the adolescents might be associated with the regional differences and cultural changes. In their study Çiçek and Aslan (14) found that the peer relations scores of high school students were moderate. They found similar results.

Smartphone addiction level of the adolescents was found to be moderate. Aktürk et al. (15) carried out a study with high school and university students and determined that their smartphone addiction level was moderate. In their study, Çalışkan et al. (16) reported that the smartphone addiction level of university students was moderate. The literature is compatible with the results of the study.

In the present study, a statistically significant difference was determined between the age groups and peer relationships of the adolescents. Peer relationships were more significant in those from the age group of 13-15 years. In the study conducted by Levpušček (17) it was determined that peer relationships were higher in the younger age group. A statistically significant difference was determined between the grade level and peer relationships of the adolescents in the study. Peer relationships of the tenth-graders were more significant. Levpušček (17) carried out a study on adolescents and found that their peer relationships decreased with increasing grade level. Erden and Yılmaz (7) reported a significant difference between the grade levels and peer relationships of the students studying in an Imam Hatip high school. In their study, Günaydın and Yöndem (18) determined a significant difference between the grade level and peer relationships of adolescents.

Table 4. Explanation of the Effect of Peer Relationships on Smartphone Addiction with Regression Analysis								
		Smartphone Addiction						
		R	R²	ΔR²	ΔF	β	t	p
Peer Relationships	Total Score	0.74	0.38	0.02	0.45	-0.01	-0.16	0.00
	Commitment	0.05	0.01	0.00	2.08	0.06	1.32	0.00
	Confidence and Identification	0.03	0.00	0.00	0.88	0.07	1.09	0.27
	Self-disclosure	0.15	0.08	0.03	0.75	-0.17	-3.02	0.00
	Loyalty	0.08	0.00	0.00	5.02	-0.04	-1.10	0.07

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In addition, Çiçek and Aslan (14) found in their study that peer relations scores of high school students differed significantly based on grade level. The difference between the mother's educational levels and peer relationships of the adolescents was statistically significant. Peer relationships of adolescents whose mother had post graduate or higher educational level were more significant. Çevik and Çelikkaleli (19) determined in their study that friendship relations were higher in adolescents whose mother had high educational level. Erden and Yılmaz (7) determined in their study that peer relationships of the Imam Hatip high school students increased as the educational levels of their mothers increased. The difference between the income level and peer relationships of the adolescents was statistically significant. Peer relationships of those with very high income level were more significant. In their study, Bayraktar and Gün (20) determined that as socio-economic level of adolescent students increased, they used internet at higher rates. Increased use of internet suggests that peer relationships may decrease. Batıgün and Kılıç (21) found that adolescents with high income level had worse peer relationships. The results of the study are compatible with those in the literature.

A statistically significant difference was found between the mother's educational levels and smartphone addiction of the adolescents. Smartphone addiction of the mothers with post graduate and higher educational level was more significant. Çevik and Çelikkaleli (19) determined in their study that internet addiction mean scores of the adolescents whose mothers were "high school" graduates were significantly higher than those of the adolescents whose mothers were "illiterate" and "primary school graduates". In addition, Çiçek, Tanriverdi, Şanlı, & Buluş (22) did not reveal a significant difference between smartphone addiction and mother's education level in their study on university students. The difference between the fathers' educational levels and smartphone addiction of the adolescents was statistically significant. Smartphone addiction was more significant among fathers with post graduate and higher educational levels. In their study, Çevik and Çelikkaleli (19) reported that internet addiction was higher in children of fathers with high educational level. This difference may be associated with high educational level of the fathers. The results revealed that the difference between the grade level and smartphone addiction of the participants was statistically significant. Smartphone addiction of the tenth-grade students was more significant. In their study, Yılmaz et al. (23) determined a statistically significant difference between the grade levels of the high school students and their internet addiction scores.

The results of the study are compatible with those of the literature.

In the present study, peer relationships of the adolescents affected the smartphone addiction. Smahel et al. (24) found in their study that peer relationships of adolescents were adversely affected by more time spent on the internet. Chou and Hsiao (25) determined that as adolescents use internet excessively, they became socially isolated and their peer relationships reduced. Savcı and Aysan (26) found in their study that peer relationships of adolescents were effective on internet addiction. Milani et al. (27) determined that weak interpersonal relationships were risk factors for increasing internet addiction.

CONCLUSION

In the present study, it was found that the peer relationship and smartphone addiction levels of the adolescents were moderate and their peer relationships affected the smartphone addiction. Based on these results, it is recommended to investigate smartphone addiction with other variables, conduct studies about the smartphone addiction levels for the parents, and organize seminars at schools by the psychiatric nurses about the common psychiatric problems during the adolescence.

DECLARATIONS

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Public Environmental and Occupational Health / Halk ve Çevre Sağlığı

Evaluation of Sociodemographic Features and Anxiety Levels of Pregnant Adolescent and Adult Pregnancy

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ABSTRACT

Objective: In this study, it was aimed to examine some sociodemographic characteristics and state trait anxiety levels of adolescent and adult pregnant women.

Methods: A total of 300 pregnant women were included in the study. 132 of the pregnants are adolescent pregnants and 168 of them are non-adolescent pregnants. The data were collected by the researcher through face-to-face interviews. Data; It consists of an information form consisting of 23 questions related to sociodemographic characteristics and reproductive health, and State and Trait Anxiety scale questions. Chi-square and student-t tests were used in the analysis.

Results: When the mean age at marriage was examined, it was found that adolescent pregnant women (16.6 ± 0.9) were much lower than non-adolescents (20.6 ± 3.1). All of the spouses of non-adolescent pregnant women are working, and 22.7% of the spouses of adolescent pregnant women do not have a job. The rate of consanguineous marriage in adolescent pregnant women was found to be 28%. The mean of the state and trait anxiety scale is inversely proportional to the education level of the participants, and the mean of the scale decreases as the education level increases. The rate of not completing primary school was quite high in adolescent pregnant women and it was determined as 43.2%. This rate is 4.2% in non-adolescent pregnant women.

Conclusion: Higher anxiety is observed due to the low level of education of pregnant adolescents who have not yet completed their own development.

Keywords: Adolescent Pregnancy, Anxiety, Conditional Anxiety, Chronic Anxiety

Ergen ve Erişkin Gebeliklerin Sosyodemografik Özellikleri ve Kaygı Düzeylerinin Değerlendirilmesi

ÖZET

Amaç: Bu araştırmada adölesan ve yetişkin gebelerin bazı sosyodemografik özelliklerinin ve durumluk süreklilik kaygı seviyelerinin incelenmesi hedeflenmiştir.

Yöntem: Çalışmaya toplam 300 gebe dâhil edildi. Gebelerin 132'si adölesan gebeler, 168'i ise adölesan olmayan gebelerdir. Veriler araştırmacı tarafından yüz yüze görüşme yoluyla toplanmıştır. Veri; Sosyodemografik özellikler ve üreme sağlığı ile ilgili 23 sorudan oluşan bilgi formu ile Durumluk ve Sürekli Kaygı ölçeği sorularından oluşmaktadır. Analizlerde ki-kare ve Student-t testleri kullanıldı.

Bulgular: Ortalama evlenme yaşı incelendiğinde adölesan gebelerin (16.6 ± 0.9) ergen olmayanlara göre (20.6 ± 3.1) çok daha düşük olduğu bulundu. Ergen olmayan gebelerin eşlerinin tamamı çalışıyor ve Adölesan gebelerin eşlerinin %22.7'si işsizdir. Adölesan gebelerde akraba evliliği oranı %28 olarak bulundu. Durumluk ve sürekli kaygı ölçeğinin ortalaması, katılımcıların eğitim düzeyi ile ters orantılı olup, eğitim düzeyi arttıkça ölçeğin ortalaması azalmaktadır. Adolesan gebelerde ilkokulu bitirmeme oranı oldukça yüksekti ve %43.2 olarak belirlendi. Ergen olmayan gebelerde bu oran %4.2'dir.

Sonuç: Henüz kendi gelişimini tamamlayamamış olan adölesan gebenin eğitim seviyesinin düşük olması nedeniyle daha yüksek kaygı görülmektedir.

Anahtar Kelimeler: Adölesan Gebelik, Anksiyete, Durumluk Kaygı, Sürekli Kaygı

The World Health Organization (WHO) adolescence is defined as the life between childhood and adulthood between the ages of 10-19. Adolescence is a period of physical, cognitive and psychosocial change and growth. It is an important phase in which the foundations of health are laid. This stage is a stage that should be considered because it is a stage in which young people interact with the environment and are affected cognitively. Adolescent pregnancy is defined as the pregnancy of people between the ages of 10-19 (1,2).

11% of births worldwide occur as a result of adolescent pregnancy. Complications of pregnancy develop in 23% of adolescents compared to non-adolescent women. And more than 90% of this occurs in developing countries(3).

Growth retardation, early and miscarriage risk, and neonatal death are among the risky outcomes that adolescent women frequently encounter during pregnancy (4).

Some risks arise due to the fact that adolescent pregnant women do not reach both physiological and psychological maturity. (5-7). According to 2018 TDHS data, it was determined that 4% of women in the 15-19 age group started to give birth to children (8).

Fear can be expressed as the anxiety of our body and mind in the face of a non-objective threat or danger. Encountering a frightening situation or an unusual object, internal and external conflicts, and difficulties in making decisions may cause anxiety (9).

Pregnancy and childbirth are a very important and unforgettable process for a woman. This process is much more important for adolescent pregnant women. As adolescents try to cope with the changes they experience without fully completing their own development, this situation will become more complicated when pregnancy is added. Adolescence is the transition period of the individual from childhood to adulthood with psychological, biological and social changes.

During this transition period, adolescent pregnant women experience much more anxiety than other pregnant women. Adolescent pregnancy is very important for public health. It is necessary and important to prevent early marriages and to minimize adolescent pregnancies as much as possible. In the study carried out; It was aimed to determine the sociodemographic characteristics, state and trait anxiety levels of pregnant adolescents and non-adolescents in Melikgazi Health Group Presidency Region.

MATERIALS AND METHODS

In this study, it was aimed to examine the sociodemographic characteristics and anxiety levels of adolescent and adult pregnant women. The research was carried out in 2008 in Istikbal Health Center, Yıldırım Beyazıt Health Center and Ahmet Gündeş Health Center Region, which are affiliated to Kayseri Melikgazi Health Group Presidency. A total of 2100 births took place in this region of health centers in 2007. By taking the adolescent pregnancy frequency of 10% (10) and the minimum acceptable value of 5%, it was calculated that 138 individuals should be recruited for the 95% confidence interval with the Epi Info 6.0 program. Pregnant women aged 19 and under were evaluated for adolescent pregnant women. It was planned to include an equal number of control groups in the research group from pregnant women who were not adolescents from the same region. Verbal consent was obtained by informing the pregnant women about the study. The questionnaire form was filled by the researcher by giving it to the pregnant women. Two forms were used to collect data in both groups. The first form consists of 11 questions about the sociodemographic characteristics of pregnant women, and the questions about reproductive health are made up of 12 questions and it is a questionnaire containing 23 questions in total. The second form is Spielberger et al. (11) state and trait anxiety scale. The scale determines state and trait anxiety levels. Each of the scales consists of two separate questions of 20 items. The analysis of the data was made with a computer using the SPSS package program. In the data, the numbers are in percentages; The means are given together with the standard deviations. Student t-test and one-way anova test were applied in the statistical comparison of the information in the data form and the scale scores. Chi-square test was used to compare qualitative data. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 300 pregnant women, 132 adolescents and 168 non-adolescents, were included in the study. The mean age of pregnant adolescents is 17.4 ± 0.5, and the mean age of non-adolescent pregnant women is 26.0 ± 5.1. The difference between the mean ages of the two groups was statistically significant (t=21.817, $p < 0.001$). While

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the mean age at marriage was 16.6 ± 0.9 in the adolescent group, it was 20.6 ± 3.1 in the non-adolescent group. The difference between the mean age at marriage was found to be statistically significant (t=16.182, p<0.001). The mean age at first gestation was 17.1 ± 0.8 in the adolescent group; In the non-adolescent group, it was found to be 21.0 ± 3.0, and the difference between the groups was statistically significant (t=16.324, p<0.001). It is the first pregnancy of all adolescent pregnant women. While it was the first pregnancy of 35.7% of the non-adolescent group, it was the second or more pregnancy of 64.3% (P <0.001 with Fisher exact chi-square test).

The status of receiving prenatal care in adolescent and non-adolescent pregnant women is given in Table 1.

The distribution of pregnant and non-adolescent pregnant women according to the place where prenatal care is taken is given in Table 2.

While the rates of receiving antenatal care from a private physician did not differ between adolescent and non-adolescent pregnant women, it was determined that the health center and delivery house were used at a higher rate by adolescent pregnant women for prenatal care.

Some sociodemographic conditions of the participants are given in Table 3.

The results of state and trait anxiety mean scores between pregnant adolescents and non-adolescents are given in Table 4.

Although the mean anxiety score is high in adolescents, the difference is not statistically significant.

Table 2. Place of Prenatal Care in Pregnant Adolescents and Non-Adolescents

Place of prenatal care	Adolescent (n=132)		Not Adolescent (n=168)		X²	p
	n	%	n	%		
Health center	111	84,1	101	60,1	20,492	<0.05
Birth house	104	78,8	12	7,1	159,993	<0.05
Private physician	44	33,3	65	38,7	0,917	>0.05
*Fisher exact chi-square test result						

DISCUSSION

Getting prenatal care is of key importance in assessing the health of the baby and the mother and in ending the birth in a healthy way. In our study, it was determined that adolescent pregnant women received more prenatal care (Antenatal care) than non-adolescent pregnant women. The study conducted by Gör Uslu and Çoban in 2020 (12) supports our study, and it was reported that 95.2% of adolescent pregnant women received prenatal care. Fulpagare et al. In the study they conducted in 2019 (13), it was determined that adolescent pregnant women received more prenatal care compared to adult pregnant women. When other studies in the literature were examined, it was found that adolescent pregnant women received antenatal care less frequently than adult pregnant women, and the findings were contrary to our study (14-16). As it can be seen in Table 2, when the place where prenatal care is taken is examined, it is seen that there is no significant difference between adolescent pregnant women and adult pregnant women in the frequency of giving birth at a private physician, but adolescent pregnant women often prefer the maternity hospital. In the study conducted by Mutlu (17), it was found that 84.5% of pregnant women were followed up in a private hospital and all of them were followed up by a doctor. 74.1% of the pregnant women gave birth in a private hospital.

Table 1. Prenatal Care Receiving Status of Pregnant Adolescents and Non-Adolescents

Status of receiving antenatal care	Adolescent		Not Adolescent		Total	
	n	%	n	%	n	%
Received	119	90,2	134	79,8	253	84,3
Not Received	13	9,8	34	20,2	47	15,7
Total	132	100,0	168	100,0	300	100,0

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Table 3. Some Sociodemographic Conditions of Pregnant Adolescents and Non-Adolescents							
	Adolescent		Not Adolescent		Toplam		
	n	%	n	%	n	%	
Educational status							
Did not complete primary school	57	43,2	7	4,2	64	21,3	X² =99,29 p<0,01
Primary school graduate	75	56,8	102	60,7	177	59,0	
High school and above	0	0,0	59	35,1	59	19,7	
Social security							
Yes	117	88,6	159	94,6	276	92,0	X² =3,623 p>0,05
No	15	11,4	9	5,4	24	8,0	
Kinship							
Yes	37	28,0	24	14,3	61	20,3	X² =8,621 p<0,05
No	95	72,0	144	85,7	239	79,7	
co-occupation							
Unemployed	30	22,7	0	0,0	30	10,0	X² =45,442 p<0,05
Worker	51	38,6	98	58,3	149	49,7	
Officer	8	6,1	17	10,1	25	8,3	
Tradesmen	43	32,6	53	31,6	96	32,0	
Spouse education							
Did not complete primary school	18	13,6	0	0,0	18	6,0	X² =45,442 p<0,05
Primary school graduate	57	43,2	93	55,4	150	50,0	
High school and above	57	43,2	75	44,6	132	44,0	
Total	132	100,0	168	100,0	300	100,0	

Tablo 4. State and trait anxiety mean scores between pregnant adolescents and non-adolescents.					
		n	Ortalama ± SS	t	p
Status	Adolescent	132	43,9 ± 7,9	1,841	>0,05
	Not Adolescent	168	42,1 ± 8,7		
Continuity	Adolescent	132	43,9 ± 7,0	1,731	>0,05
	Not Adolescent	168	42,5 ± 7,4		

In our study, as can be followed from Table 3, when some sociodemographic statuses of pregnant adolescents and non-adolescents were examined, it was determined that there was a significant difference between the education levels of pregnant adolescents and adult pregnants, and 43.2% of pregnant adolescents did not graduate from primary school. When the kinship status with the spouse was examined, 28% of the adolescent pregnant women had consanguineous marriages, and this rate was found to be 14.3% in adult pregnant women. The difference was found to be statistically significant. When evaluated in terms of spouse occupation, 22.7% of spouses of adolescent pregnant women do not have any job, while spouses of adult pregnant women are not unemployed(p<0.05). In the study conducted by Oğuz in 2018, it was reported that 1.4% of adolescent pregnant women and 5% of adult pregnant women were illiterate. While 20.5% of adolescent pregnant women do not have any social security, this rate was found to be 5.5% in adult pregnant women (18). In our study, it was determined that although the state and trait anxiety mean scores of adolescent pregnant women were higher than the non-adolescent group, the difference was not statistically significant. Among the reasons why adolescent pregnant women and their spouses have lower education and socioeconomic levels compared to adult pregnant women, they experience more economic difficulties, and the fact that they have not yet fully completed their own development can be counted among the reasons why their state and trait anxiety mean scores are high.

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When the literature was searched, it was stated that women with low socio-economic status during pregnancy showed more frequent depressive symptoms. (19,20). Akbas et al. Contrary to our study, there was no relationship between income level and depression and anxiety in their study (21). In the study conducted by Can and Çakır on pregnant women, it was determined that the depression and anxiety scores decreased when the monthly income was high (22).

CONCLUSION

In this study, in which the sociodemographic characteristics and state trait anxiety levels of adolescent and non-adolescent pregnant women were evaluated; Average monthly income is higher in non-adolescent pregnant women. While 22.7% of the spouses of pregnant adolescents are unemployed, there are no unemployed spouses of non-adolescent pregnant women. The education level of spouses of non-adolescent pregnant women is higher. The rate of consanguineous marriage is higher in adolescent pregnant women. The rate of those who do not have social security is higher in adolescent pregnant women. 43.2% of pregnant adolescents and 4.2% of non-adolescents did not complete primary school. Prenatal care is higher in adolescent pregnant women. Adolescent pregnant women need information, guidance, help and support about pregnancy and childbirth. Pregnancy, which causes many difficulties in every period of a woman's life, affects the person physically and psychologically in a very negative way, especially if it is experienced in adolescence. A pregnancy and parenting program should be established for adolescent mothers and adolescent fathers, and they should be informed about education, employment, paternity skills and contraception.

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   Health Policy and Services / Sağlık Politikaları ve Hizmetleri

The Effect of Trust in Politicians and Perceptions of Macro Control on Attitudes towards Vaccines During the Covid-19 Pandemic Process

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ABSTRACT

Objective: The purpose of this study is to investigate the effect of trust in politicians and perceptions of macro control on positive and negative attitudes towards vaccines during the Covid-19 pandemic process.

Method: This is a cross-sectional field study. In the research, convenience sampling and snowball sampling methods were used together. 1198 Turkish citizens at the age of 18 and over filled out an online questionnaire between May 6 and June 6, 2021. The questionnaire form consists of the scales of Trust in Politicians, Perception of Pandemic Macro Control, Attitudes towards Vaccines in addition to the demographic variables. In the analysis of the data, frequency, reliability, correlation, and regression analyzes were performed using the SPSS V.26 program, respectively.

Results: Trust in politicians during the pandemic process has a statistically significant and positive effect on the perception of pandemic macro control. While trust in politicians and perception of pandemic macro control have a statistically significant and positive effect on positive attitude towards vaccines, they have a negative effect on a negative attitude towards vaccines.

Conclusion: It was concluded that the trust in politicians and the perception of the adequacy of macro control measures taken by governments play an important role in people's adopting a positive attitude towards the developed vaccines to fight against the Covid-19, which has turned into a global pandemic.

Keywords: Trust in Politicians, Perception of Pandemic Macro Control, Attitudes towards Vaccines

Covid-19 Pandemisi Sürecinde Politikacılara Duyulan Güven ve Makro Kontrol Algılarının Aşıya Karşı Tutum Üzerine Etkisi

ÖZET

Amaç: Bu araştırmanın amacı, Covid-19 pandemisi sürecinde politikacılara duyulan güven ve makro kontrol algılarının aşıya karşı olumlu ve olumsuz tutum üzerine etkisinin incelenmesidir.

Yöntem: Araştırma kesitsel tipte bir saha araştırmasıdır. Araştırmada kolayda örnekleme ve kartopu örnekleme yöntemleri birlikte kullanılmıştır. 6 Mayıs-6 Haziran 2021 tarihleri arasında 18 yaş ve üzeri 1198 Türk vatandaşı çevrimiçi bir anket doldurmuştur. Anket formu demografik değişkenlerin yanısıra Politikacılara Güven, Salgın Makro Kontrol Algısı, Aşıya Karşı Tutum ölçeklerinden oluşmaktadır. Verilerin analizinde, SPSS V.26 programı kullanılarak sırasıyla frekans, güvenilirlik, korelasyon ve regresyon analizleri yapılmıştır.

Bulgular: Pandemi sürecinde politikacılara yönelik güven, salgın makro kontrol algısını istatistiksel olarak anlamlı ve pozitif yönde etkilemektedir. Politikacılara güven ve salgın makro kontrol algısı aşıya karşı olumlu tutumu istatistiksel olarak anlamlı ve pozitif yönde etkilerken aşıya karşı olumsuz tutumu negatif yönde etkilemektedir.

Sonuç: Küresel bir salgına dönüşen Covid-19 ile mücadele etmek için bireylerin geliştirilen aşıya karşı olumlu tutum benimsemesinde politikacılara duyulan güven ve hükümetler tarafından alınan makro kontrol önlemlerinin yeterliliğine yönelik algı önemli rol oynadığı sonucuna ulaşılmıştır.

Keywords: Politikacılara Güven, Salgın Makro Kontrol Algısı, Aşıya Karşı Tutum

The whole world is under the threat of the Severe Acute Respiratory Syndrome Coronavirus 2 -SARS-C0V-2- (Covid-19) pandemic since the end of 2019. In line with the statements of the World Health Organization (WHO) that reducing the effect of Covid-19 should be a top priority for governments, most countries are taking strict measures to slow down the spread of the disease. The main measures taken are mask-social distancing-hygiene rule, implementation of movement restrictions in social and economic sectors, lockdown practices, avoiding travel unless it is necessary, curfews, distance education and work, flexible working hours and widespread vaccination (1, 2, 3, 4, 5).

Covid-19 pandemic is perceived as a real threat by individuals as it limits their perception of personal control and risks the lives of themselves and their beloved ones (6). High risk and realization of the threat direct people to adhere to the measures taken by governments during the process of the fight with pandemics (7, 8). In other words, when people feel that they have lost their control on their own lives, they tend to adapt to the macro measures to satisfy their needs (9). In the pandemic period when personal control is insufficient, people's perceptions of trust in resources such as government and health authorities, which are expected to provide macro control, are important in terms of adapting to measures in the fight against the pandemic (10).

In addition to personal and macro measures within the fight against infectious diseases, vaccination rates and immunity level of the communities play important role to take the disease under control (11). According to WHO data, 2-3 million deaths due to infectious diseases are prevented each year thanks to vaccination (12). The WHO carries out validity and reliability studies in order to take the Covid-19 pandemic under control through vaccination and emphasizes that vaccination is crutial to end the Covid-19 pandemic. In this context, it was announced by the WHO that as of June 3, 2021, Sinovac, Pfizer/BionTech, AstraZeneca/Oxford vaccines, Johnson and Johnson, Moderna and Sinopharm vaccines meet the criteria for safety and effectiveness (13). Sinovac and Biontech vaccines are applied in Turkey as the Covid-19 vaccines (14).

Although vaccination is important in controlling pandemics, for many reasons such as distrust in health system components, attitudes towards healthcare professionals, distrust in pharmaceutical companies, belief that vaccine content is harmful, lack of information about the effectiveness of vaccines, negative information in the media, possible future side effects of vaccines, concerns about the effects of vaccines, attitudes of families towards vaccines, fear of vaccines, etc., people have negative attitudes towards vaccines such as vaccine hesitancy, reluctance to be vaccinated, and vaccine rejection (15, 16, 17, 18, 19, 20).

Despite studies on vaccination, the pandemic keeps spreading and the number of deaths increases day by day. Despite the deadly consequences of the Covid-19 disease, people's avoidance from vaccination negatively affects the success of the fight against the pandemic. Therefore, it becomes important to investigate the factors that affect people's attitudes towards vaccines. In this context, the purpose of this study is to determine the effect of trust in politicians and macro control perceptions on the attitude towards vaccines.

METHODS

Study Design and Participants

This study is a cross-sectional field study designed in descriptive-relational type. The population of the study consists of individuals aged 18 and over who are citizens of the Republic of Turkey. In the study, convenience sampling and snowball sampling methods were used together. An online questionnaire, created on Google Forms, was sent to approximately 2,000 people who voluntarily agreed to participate in the study. In addition, the participants were asked to share the questionnaire form with other people over the age of 18. The study data were collected from 1321 participants from 81 provinces of Turkey in a one-month period between May 6 and June 6, 2021. The data of 87 participants who gave wrong answers to the control question and 36 participants who marked all statements in the scales with the same agreement level were excluded from the analysis. Therefore, the data from 1198 participants were analyzed in the study.

Measures

The questionaire form consists of the scales of Trust in Politicians, Perception of Pandemic Macro Control, Adherence to Measures, Attitudes towards Vaccines in addition to the demographic variables. There are 8 questions about the demographic features of the participants. The scale of Trust in Politicians was developed by Boukes and Boomgaarden (2016). In the scale, there are 10 statements under one dimension for honesty and reliability of politicians. There are 5 reverse coded statements in the scale. Cronbach's Alpha (Cα) coefficient of the scale is 0.87 (21). The scale of Pandemic Macro Control Perception was

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developed by Çırakoğlu (2011) for H1N1 virus. There are 5 statements in the scale. Cα coefficient of the scale is 0.83 (22). The scale in question was adapted for Covid-19 in this study. The Scale of Attitudes towards Vaccines was developed by Çırakoğlu (2021). The scale developed in order to measure positive and negative attitudes of the participants towards vaccines consists of 9 statements in two sub-dimensions. There are 4 statements in the dimension of positive attitude towards vaccines. Cα coefficient of this sub-dimension is 0.85. There are 5 statements in the dimension of negative attitude towards vaccines and all of these statements are reverse coded. Cα coefficient of this sub-dimension is 0.67 (22). The scale was adapted for Covid-19 in this study. All scales in the study were used as 5-point Likert scale.

Data Analysis
In the analysis of the data, frequency analysis, reliability analysis, correlation analysis and regression analysis were performed using SPSS V.26 program, respectively. Cα>0.70 was accepted as the reliability of the scales used in the study (23). Skewness and Kurtosis values (±1,500) were taken into account in normality hypothesis of the data (24). In the evaluation of the findings, <0.05 significance level and 95% of trust frequency were accepted.

Ethical Considerations
Before starting the research, approved by the Usak University Social and Human Sciences Scientific Research and Publication Ethics Committee with the decision of 2021/96 dated 06.05.2021. Additionally, before starting the online questionaire, the participants confirmed that they voluntarily participated in the study after reading the information about the purpose of the study and the fact that the data to be collected will be used only for scientific purposes and their personal information will be kept confidential.

RESULTS
The descriptive statistics of the individuals participating in the study are summarized in Table 1.

1198 individuals aged 18 and over from 81 provinces of Turkey participated in the study. 56.2% of the participants are female and 43.8% are male. Considering the marital status of the participants, 60.1% are married and 39.9% are single. 59.9% of the participants are between the ages of 18-29 and their age average is 29.47±10.02. 65.4% of the participants are university graduates. 30.2% of the participants are students (Table 1).

Table 1. Socio-demographic Characteristics (n=1198)			
Variable		**N**	**%**
Gender	Female	673	56.2
	Male	525	43.8
Marital Status	Married	478	60.1
	Non-Married	720	39.9
Age Min= 18 Max= 78 Mean= 29.47 Sd=10.02	18-29	718	59.9
	30-39	268	22.4
	40-49	150	12.5
	50-59	51	4.3
	60 and above	11	0.9
Educational Status	Primary education	78	6.5
	High school	171	14.3
	University	784	65.4
	Master	120	10.0
	Doctorate	45	3.8
Profession	Student	362	30.2
	Public personnel	189	15.8
	Private sector employee	148	12.4
	Health personnel	105	8.8
	Entrepreneur	86	7.2
	Teacher	71	5.9
	Public worker	65	5.4
	Academician	59	4.9
	Housewife	52	4.3
	Unemployed	43	3.6
	Retired	18	1.5
Total		**1198**	**100**

Descriptive statistics regarding the scales used in the study are presented in Table 2. The average of the scale of trust in politicians is 2.26±0.922, the average of the scale of pandemic macro control is 2.69±0.935, the average of the positive attitude towards the vaccine is 3.23±1.271, and the average of the negative attitude towards the vaccines is 2.26±0.889. Since the Skewness and Kurtosis values of the scales in the study were between -1.004 and 0.456, it was accepted that the research data had a normal distribution. Since the Cronbach's Alpha coefficient of all scales used in the study was Cα>0.70, the scales were accepted as reliable (Table 2).

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Table 2. Descriptive Statistics Regarding the Scales							
Scale	**Min**	**Max**	**Mean**	**Sd**	**Skewness**	**Kurtosis**	**Cronbaach's Alpha (Cα)**
Trust in Politicians	1.00	5.00	2.26	.922	.456	-.223	.891
Perception of Pandemic Macro Control	1.00	5.00	2.69	.935	.218	-.539	.824
Positive attitude towards the vaccine	1.00	5.00	3.23	1.271	-.261	-1.004	.937
Negative attitude towards the vaccine	1.00	5.00	2.69	.889	.339	-.013	.790

Results of correlation analysis performed in order to determine the correlation between variables are presented in Table 3.

While there exists a statistially significant, positive, lineer and poor correlation between the trust in politician variable and pandemic macro control perception (r = 0.482, p<0.001), positive attitude towards vaccines (r = 0.269, p<0.001), there exists a statistically significant, negative, lineer and poor correlation with negative attitude towards vaccines (r = -0.230, p<0.001). While there exists a statistically significant, positive, lineer and poor correlation between pandemic macro control perception variable and positive attitude towards vaccines (r =0.411, p<0.001) variables, there exists a statistically significant, negative, lineer and poor correlation with negative attitude towards vaccines (r = - 0.307, p<0.001).

In accordance with the purpose of the study, 3 different regression model was established. Enter mode was used in regression analysis. Correlation value (r = 0.482) between the independent variables of the study is smaller than 0.7. In addition, Variance Inflation Factor (VIF) value (VIF = 1.302) is smaller than 10 and tolerance value (Tolerance = 0.768) is larger than 0.10 in multiple lineer regression analyses performed in the study. It was determined that these values are acceptable and there is no multicollinearity problem in existing sample (25). Results of the relevant regression analyses are presented in Table 4 and Table 5.

Table 3. Correlation Analysis Results Between Variables						
Variables			**1**	**2**	**3**	**4**
1	**Trust in Politicians**	Pearson Correlation	1			
		Sig.	0.001			
2	**Perception of Pandemic Macro Control**	Pearson Correlation	0.482	1		
		Sig.	0.001			
3	**Positive attitude towards the vaccine**	Pearson Correlation	0.269	0.411	1	
		Sig.	0.001	0.001		
4	**Negative attitude towards the vaccine**	Pearson Correlation	-0.230	-0.307	-0.573	1
		Sig.	0.001	0.001	0.001	

Table 4. The Result of the Regression Analysis on the Effect of Trust in Politicians on the Perception of Pandemic Macro Control						
Dependent variables	**Independent variables**	**B**	**SE**	**β**	**t**	**p**
Perception of Pandemic Macro Control (1)	**Costant**	1.589	.063		25.343	.001
	Trust in Politicians	.488	.026	.482	19.002	.001
	R= .482; R²= .232; F= 361.069 (p=.001)					

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Table 5. The Result of the Regression Analysis on the Effect of Trust in Politicians and the Perception of Pandemic Macro Control on Attitudes Towards Vaccines.

Dependent variables	Independent variables	B	SE	β	t	p
Positive attitude towards the vaccine (2)	Costant	1.598	.110		14.558	.001
	Trust in Politicians	.128	.041	.092	3.086	.002
	Perception of Pandemic Macro Control	.499	.041	.367	12.244	.001
	R= .419; R²= .176; F= 127.465 (p=.001); Tolarence= .768; VIF= 1.302					
Negative attitude towards the vaccine (3)	Costant	3.579	.080		44.780	.001
	Trust in Politicians	-.103	.030	-.107	3.408	.001
	Perception of Pandemic Macro Control	-.244	.030	-.256	8.197	.001
	R= .321; R²= .103; F= 68.804 (p=.001); Tolarence= .768; VIF= 1.302					

The regression model established for the effect of trust in politicians variable on the perception of pandemic macro control variable is statistically significant (F = 361.069, p<0.001). According to simple lineer regression model, it was determined that trust in politicians variable has a statistically significant and positive effect on the perception of pandemic macro control (β = 0.488, p<0.001) variable. Trust in politicians variable can explain 23.2% of the change in the perception of pandemic macro control variable (R² = 0.232).

The regression model established for the effect of trust in politicians and perception of pandemic macro control variables on positive attitude towards vaccines variable is statistically significant (F = 127.465, p<0.001). According to multi lineer regression model, trust in politician (β = 0.092, p<0.002) and perception of pandemic macro control (β = 0.367, p<0.001) variables have a statistically significant and positive effect on positive attitude towards vaccines variable. Trust in politicians and perception of pandemic macro control variables can explain 17.6% of the change in positive attitude towards vaccines variable, which is a dependent variable (R² = 0.176).

The regression model established for the effect of trust in politicians and perception of pandemic macro control variables on negative attitude towards vaccines variable is statistically significant (F = 68.804, p<0.001). According to multi lineer regression model, trust in politicians (β = -0.107, p<0.001) and perception of pandemic macro control (β = -0.256, p<0.001) variables have a statistically significant and negative effect on negative attitude towards vaccines variable. Trust in politicians and perception of pandemic macro control variables can explain 10.3% of the change in negative attitude towards vaccines variable, which is a dependent variable (R² = 0.103).

DISCUSSION

With the emergence of new virus variants during the Covid-19 pandemic process, there is a rise in the number of cases again and the course of the disease also changes. For that reason, the need for measures against the virus and the importance of these measures gradually increases. In addition to the measures, one of the biggest trump cards in the hands of human beings in the fight against the pandemic is considered to be vaccination and ensuring social immunity. Although there is an increase in the positive approach towards vaccines and vaccination in Turkey and in the world, negative attitudes and anti-vaccination still stand as an obstacle to social immunity. In this process, it is inevitable that macro control perceptions of individuals towards the pandemic and the trust in politicians who are in the decisive position in the health policies of the countries will have an effect on the attitudes towards vaccines. In this context, the purpose of this study is to investigate the effect of trust in politicians and perception of macro control during the Covid-19 pandemic process on positive and negative attitudes towards vaccines.

The first finding of the study is that as the level of trust of the participants in politicians and policy makers increases, the perception of macro control towards pandemic increases as well. Similarly, it was determined in a study conducted in Norway and Sweden in early periods of the pandemic that participants highly trust in governments and health services and believe that the decisions for macro measures about the pandemic are based on scientific evidences (26). Low levels of trust in political decision makers lead to the development of perceptions of lack of macro control and individuals to find ways to protect their own interests autonomously (27). According to this finding of the study and the current literature, individuals' feelings of trust in politicians during the pandemic process positively affect their perceptions of the adequacy of macro control measures regarding the pandemic.

The final finding of the study is that the increase in the participants' trust in politicians and the adequacy of the macro control measures taken for the epidemic has a statistically significant positive effect on the positive attitude towards the vaccines and a statistically significant negative effect on the negative attitude towards the vaccines. Similar to this finding of the study, it was concluded in a study by Lazarus et al. (2020) individuals' trust in information from the sources of governments has a positive effect on vaccination (28). In a study by Quinn et al. (2016) it was determined that trust in government has a positive effect on positive attitude towards vaccines (29). Baumgaertner, Carlisle, and Justwan (2018) stated in their study on pertussis, measles and flu vaccines that ideological and political views, and therefore the trust in politicians, who correspond to these views, affect attitudes towards vaccines.In the concerning study, it was determined that the attitude of the politicians whom the participants trust towards vaccines causes the individuals to adopt a positive or negative attitude towards vaccines (30). Likewise, in the study by Fridman, Gershon and Gneezy (2021) it was confirmed that this is also valid for the Covid-19 vaccine and other types of vaccines (31). In the study by Criss et al. (2021), in which the tweets of Twitter users in the USA during the Covid-19 period were examined, it was seen that the attitudes of politicians and the trust in them had an effect on the anti-vaccination and attitude towards vaccines (32). Therefore, it is possible to say that the increase in the level of trust in ideological figures, governments and politicians, who are the representatives of these political structures, has a positive effect on the positive attitude towards vaccines.

CONCLUSION

The Covid-19 pandemic continues to spread despite individual, organizational, national, and international measures and efforts to expand vaccination studies. As the pandemic continues, the number of infected patients and deaths due to the Covid-19 increase. That being said, due to the fact that some people hesitate about vaccination, fear of vaccination and refusal to be vaccinated negatively affect the success of the fight against the pandemic. Therefore, investigating the factors that affect people's attitudes towards vaccines is important for the success of the fight against the pandemic.

It was concluded in the study that individuals' trust in politicians and their perceptions of the adequacy of the macro control measures regarding the pandemic contributed to their positive attitudes towards vaccines. In addition,

trust in politicians and perception of macro control reduce negative attitudes towards vaccines. In the context of the results obtained in the research, it can be said that it is important to develop the feeling of trust of the society towards policy makers and health-related authorities in the fight against the Covid-19 pandemic. In order to gain the trust of the society and fight with the pandemic, politicians and health authorities should share accurate and up-to-date information transparently, explain the measures with their scientific sources, quickly eliminate the environment of uncertainty and misinformation, ensure unity by leaving political concerns and conflicts aside, and provide consistent messages to the society and people should be provided with access to information resources. In addition, in the pandemic process where individual control is insufficient, it is necessary to raise awareness of the society, to create a social unity for trying to adhere to macro measures, and to ensure that individuals develop a positive attitude towards the Covid-19 vaccines. It was concluded in the study that it is important for politicians to create a feeling of trust in the success of the fight against the Covid-19 and to improve the perceptions of the society about the adequacy of the macro control measures based on science-related to the pandemic.

This study has some limitations as in all other ones. First, the study limits the generalization of the results as it was designed as cross-sectional and a convenience sampling method was used. A second limitation is the small number of participants aged 60 and over and retired in the sampling of the study. Future studies may focus on people over 60 and retired. A third limitation is the small number of participants infected and vaccinated with Covid-19, as the study was conducted during the early stages of vaccine administration. With the widespread vaccination, it is thought that examining the attitudes of those who are vaccinated and those who are not and their behavior to adhere to measures will make a significant contribution to the literature. Finally, it can be recommended to investigate different factors that affect attitudes towards vaccines for future studies.

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