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AMELIORATIVE EFFECTS OF BAICALIN AGAINST EXPOSURE TO FLUMETHRIN IN MALE RATS*
ERKEK RATLARDA FLUMETRİN MARUZİYETİNE KARŞI BAİKALİNİN İYİLEŞTİRİCİ ETKİLERİ

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ABSTRACT

Flumethrin is a pyrethroid insecticide, while baicalin is a flavonoid with antioxidant, anti-inflammatory, and anticarcinogenic properties. The aim of this study was to investigate the effects of baicalin on biochemical parameters and lipid peroxidation flumethrin-induced in rats. In the study, 42 rats were divided in to six groups with each group comprising seven rats. Flumethrin was administrated 15 mg/kg b.w. to second group, flumethrin+baicalin 50 mg/kg b.w. was administrated to third group, flumethrin+baicalin 100 mg/kg b.w. was administrated to fourth group, baicalin 50 mg/kg b.w. was administrated to fifth group, and baicalin 100 mg/kg b.w. was administrated to sixth group. After, blood and tissue samples were collected for biochemical and histopathological evaluations. According to obtained results, when flumethrin-induced group was compared to control, alkaline phosphatase, cholesterol, blood urea nitrogen, uricacid and total protein levels significantly decreased. Also, kidney catalase and plasma glutatione peroxidase, liver catalase and superoxide dismutase activities decreased, but both kidney and liver nitric oxide and melon dialdehyde levels increased in flumethrin-induced group. Flumethrin caused to histopathological alterations in tissues. On the other hand, statistically, kidney catalase and plasma glutation eperoxidase, liver catalase and superoxide dismutase activities increased, but nitricoxide and melon dialdehyde levels decreased in all groups given baicalin. In additionally, baicalin affected to some biochemical parameters ($p<0.05$) and regressed to tissue damage. The obtained biochemical results were consistent with histopathological results. In conclusion, this study suggests that Baicalin can ameliorate oxidative stress and tissue damage in flumethrin-induced subacutet oxication in rats.

Keywords: Antioxidant, baicalin, flumethrin, lipid peroxidation, toxicity.

ÖZ

Baikalin antioksidan, antiinflamatuar ve antikarsinojenik özelliklere sahip bir flavonoidken, flumetrin bir piretroid insektisittir. Bu çalışmanın amacı, flumetrin ile indüklenmiş ratlarda baikalinin biyokimyasal parametrelere ve lipid peroksidasyonuna etkilerini araştırmaktı. Çalışmada 42 adet rat, her grupta yedi adet rat olacak şekilde altı gruba ayrıldı. Flumetrin ve baikalin mısır yağı içinde tek doz oral gavaj yoluyla 28 gün boyunca verildi: Kontrol grubuna mısır yağı uygulandı. Flumethrin 15 mg/kg c.a. ikinci gruba, flumetrin+baikalin 50 mg/kg c.a. üçüncü gruba, flumetrin+baikalin 100 mg/kg c.a. dördüncü gruba, baikalin 50 mg/kg c.a. beşinci gruba, baikalin 100 mg/kg c.a. altıncı gruba verildi. Daha sonra kan ve doku örnekleri biyokimyasal ve histopatolojik değerlendirmeler için alındı. Elde edilen sonuçlara göre, flumetrin verilen grup kontrol ile karşılaştırıldığında kolesterol, alkalen fosfataz, total protein, üre ve ürik asit düzeyleri anlamlı seviyede azaldı. Ayrıca flumetrin alan grupta böbrek süperoksit dismutaz ve glutatyon peroksidaz ile karaciğer süperoksit dismutaz ve katalaz aktiviteleri azaldı, ancak hem karaciğer hem de böbrek melondialdehit ve nitrik oksit seviyeleri arttı. Flumetrin dokularda histopatolojik değişikliklere neden olmuştur. Öte yandan, baikalin verilen tüm gruplarda istatistiksel olarak böbrek süperoksit dismutaz ve glutatyon peroksidaz ile karaciğer süperoksit dismutaz ve katalaz aktiviteleri arttı, ancak nitrik oksit ve melondialdehit düzeyleri azaldı. Ayrıca baikalin bazı biyokimyasal parametreleri etkiledi ($p<0.05$) ve doku hasarını azalttı. Elde edilen biyokimyasal sonuçlar histopatolojik sonuçlarla uyumludur. Sonuç olarak, ratlarda flumetrin ile oluşturulan subakuttoksikasyonda, Baicalin oksidatif stresi ve doku hasarını iyileştirebilir.

Anahtar kelimeler: Antioksidan, baikalin, flumethrin, lipid peroksidasyonu, toksisite.

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INTRODUCTION

Pyrethroids are the synthetic compounds derived of pyrethrins whic hare natural organic insecticides procured from the *Chrysanthemum cinerariaefolium* plant. They exhibit fewer toxic properties than other insecticides such as carbamate and organophosphate in mammals and are resistant to sunlight in the environment for a longtime. There fore, they are generally morepreferred to againstec to parasites. Pyrethroids affect the peripheral and central nervous systems. These insecticides cause inhibition of voltage-dependent sodium channels located in the cell membrane, showing rapid knock-down properties and cause temporary paralysis and death of insect. According to the differences in their chemical structures and their mechanism of action, pyrethroids are divided into two groups; Type I and Type II.[1] Flumethrin (FL) is, Type II synthetic pyrethroid,an oil-soluble insecticide used in veterinary medicine to control ectoparasites. Flumethrin is a neurotoxic substance, and its activity takes place on sodium and chloride channels of insects. Flumethrin inhibites to voltage-dependent Na channels and increases the passage of Na ions through the nerve membrane. Continuing ion permeability for a long time provides a permanent depolarization. In neurons cause repeated and prolonged stimulation on muscles and organs as sodium continues to enter the cell. This situation has a lethal effect on insects.[2,3]

The antioxidant enzymes that catalyse (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) arean essential defense against the harmful effects of free radicals. Superoxide radicalsare converted into hydrogen peroxide (H_2O_2) and molecular oxygen by SOD. The H_2O_2, a harmful metabolite, is converted to water and oxygenby CAT. The GSH-Pxuses glutathione as electron source and it prevents the formation of hydroxyl (OH) from H_2O_2. These reactions are antioxidant defense system for cells. Disruptionsin the antioxidant defence system may cause to the formation of oxidative stress. As a result of these disruptions, different aldehydes are formed. Malondi aldehyde (MDA) is the mostactive worker among these aldehydes. The amounts of MDA and nitricoxide (NO) are considered to be the most important indicator of membrane lipid peroxidation resulting from the interaction of cell membrane and the reactive oxygen species (ROS).[4,5] Pesticides may induce to oxidative stress, too.[6]

When previous studies on flumethrin are reviewed, there are only few studies reporting that it affects oxidant/antioxidant balance and hematological parameters.[7-10]

Flavonoids are polyphenolic compounds found in many fruits and vegetables.[11] Baicalin (BA), a flavonoid, is found in severalplantspecies in the *Scutellaria* genus, such as *Scutellariabaicalensis* and *Scutellarialateriflora*. In many studies, it has been stated that baicalin has anti-inflammatory, antibacterial, neuroprotective, antiapoptotic, and antioxidant properties.[12-18] Pharmacokinetic studies have shown that baicalin is hydrolyzed in the gastrointestinal tract,[19] enterohepatic recycling,[20] and transported across the cell membrane via a carrier.[21] Baicalin has a limited bioavailability of 2.2%. This leads to its limited clinical efficacy.[20] However, the absorption of baicalin in the stomach is moderate. Following its entry into metabolism, it is hydrolyzed to baicaleine, the aglycone form, bythe β glucuronidase enzyme produced by intestinal bacteria.[22]

In the present study, the effects of baicalin on blood biochemical parameters in serum and lipid peroxidation parameters in liver and kidney tissues were investigated on flumethrin-induced subacute toxicities in rats. In addition, histopathological evaluations were also performed on liver and kidney tissues.

MATERIAL AND METHODS

Chemicals

Baicalin (98%, 5 g, Med Chem Express, HY-N0197), flumethrin (Bayticol, 1000 mLpour-on solution of 1%, Bayer), ketamine (Ketals, 500 mg, 10 mL solution for injection, Pfizer), xylazine (Rompun, 2%, 23.32 mg/mL, Bayer), TBA (Sigma, T5500), nitrate reductase (Sigma, N7265), TCAA (Sigma, T6399), Griess reagent (Sigma, G4410), phosphate buffer (Sigma, P3619), *n*-butanol (Sigma, 281549), EDTA (Sigma, E5134), H_2O_2solution (Sigma, 216763), xanthine oxidase (Sigma, X1875), NaN_3 (Sigma, S2002), $CuCl_2$ (Sigma, N5130), NADPH (Sigma, N7505), FAD (Sigma, F6625), glutation reductase (Sigma, G4251) were supplied from related to companies.

Animals

The this study was carried out with the ethics committee approval dated 09.10.2019 and numbered 19/171 given by the Erciyes University, Animal Experiments Local Ethics Committee.

The rats used in the study were obtained from Erciyes University, Experimental and Clinical Research Center (DEKAM). Forty-two male *Wistar Albino* rats, aged 16-18 weeks, and weighing 250-350 g, were used. The rats were divided into six groups, with seven animals in eachcage. Animals were fed with pelletfeed *ad-libitum.* They were housed under suitable conditions[(controlled temperature (21±2°C), humidity (%50±5), air change (12 cyclesperhour), light (12 hourlight, 12 hoursdark)] by the research center.

Experimental design and model

The animals were divided into six groups with seven animals in each group, and a total of 42 rats were used. The study continued for 28 days. Group 1 was used as the control group. This group was given cornoil by oral gavage. Group 2 was given FL 15 mg/kg b.w. in cornoil by oral gavage.[7]Group 3 was given FL 15 mg/kgb.w. and a single dose of 50 mg/kg b.w. incornoil by the same route. Group 4 was given FL 15 mg/kg and BA 100 mg/kg. Group 5 was given BA 50 mg/kg and group 6 was given BA 100 mg/kg.

Taking the samples

At the end of the experiment, ketamine + xylazine anesthesia was applied to all groups. After ward, blood samples were collected into gel tubes by cardiac puncture. The rats were euthanized, and tissue samples were taken. The blood samples were centrifuged at 4000 *rpm* for 10 minutes and kept at +4 ºC and -20 ºC throughout the experiment. Liver and kidney tissues were quickly removed and stored at -20 ºC for oxidants/antioxidants analysis.

Determination of serumbiochemical parameter levels

Some biochemical parameter levels (AST, ALT, ALP, LDH, total protein, cholesterol, triglyceride, BUN, uricacid and creatinine) were determined in the blood, and analyses were performed by A Roche Cobas kit and an auto analyzer.

Determination of lipid peroxidation parameters in liver and kidney tissues

Liver and kidney tissues were homogenized in ice-cold with a pH of 7.2 phosphate buffer at a ratio of 1:4 in a mechanical-tipped homogenizer for half a minute at 20000 *rpm* for the measurement of lipid peroxidation parameters. Next, the obtained mixture was homogenized for half a minute with an ultrasonic homogenizer. Then, the homogenates were centrifuged at 20000 *rpm* for one hour in a centrifuge set at +4 ºC, and the clear upper part was taken in to the Eppendorf tubes. The tubes were stored in the freezer at -20 ºCuntil the time of analysis.

Tissue protein,[23,24] MDA,[25] SOD,[26] NO,[27] GSH-Px,[28] and CAT[29] were analyzed according to the methods described.

Histopathological evaluation

Liver and kidney tissues were taken into 10% formaldehyde. Tissues detected in formaldehyde for at least 48 hours were trimmed and placed in tissue cassettes. The taped tissues were washed under tap water for eight hours and then dehydrated by passing through serial alcohols. Dehydrated tissues were made transparent by passing through xylene and then blocked in paraffin. Five-micron sections from each of the blocks were taken on a slide with a microtome. Tissues on the slide were stained with Hematoxylin-Eosin (H&E), and histopathological changes in the tissues were evaluated.

Statistical evaluation

The SPSS program (SPSS, version 21.0, IBM Corp.) was used for all statistical analyses. Statistical analysis of the data was calculated by one-way analysis of variance (ANOVA). Differences between groups were determined using the Tukey test. Analysis results were given as arithmetic mean±standard deviation. The value of $p<0.05$ was taken as the level of significance.

RESULTS

Effects of baicalin and flumethrin on biochemical parameters

Obtained results were shown in tables. Triglyceride, cholesterol, BUN, creatinine, and uricacid (Table 1); AST, ALT, ALP, LD Hand total protein levels (Table 2).

According to the obtained data from this study, compared to the groups in rats, the serum triglyceride levels were nostatistically significant change. However, cholesterol and BUN levels were statistically significantly lower in all groups compared to the control group ($p<0.05$). In addition, creatine level was similar to

Table 1. Effects of baicalin and flumethrin administration on serum triglyceride, cholesterol, BUN, creatinine and uricacid levels in rats

Groups	Triglyceride (mg/dL)	Cholesterol (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Uricacid (mg/dL)
G1	148.00±51.42	67.57±9.46^{b}	22.05±2.26^{d}	0.38±0.02^{a,b}	1.34±0.46^{b}
G2	110.42±34.84	57.00±5.91^{a,b}	18.27±1.81^{a,b,c}	0.37±0.03^{a,b}	0.92±0.09^{a,b}
G3	78.85±22.31	53.71±4.92^{a}	16.27±1.35^{a,b}	0.33±0.02^{a,b}	0.78±0.17^{a}
G4	83.42±28.61	57.42±4.96^{a,b}	16.04±2.3^{a}	0.33±0.01^{b}	0.81±0.16^{a}
G5	135.57±62.18	61.42±6.80^{a,b}	19.48±1.24^{c,d}	0.38±0.03^{a}	1.01±0.35^{a,b}
G6	119.57±53.12	56.42±7.80^{a}	19.07±1.59^{b,c}	0.37±0.04^{a,b}	1.00±0.22^{a,b}
P values	0.35	0.01	0.00	0.01	0.00

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b,c,d} The same letters in the same column in dicatesimilarity between groups, different letters indicate difference between groups ($p<0.05$).

Table 2. Effects of baicalin and flumethrin administration on serum AST, ALT, ALP, LDH, total protein and albümin levels in rats

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	LDH (U/L)	Total protein (g/dL)
Group 1	124.00±30.33	63.00±15.73	313.85±78.70^{b}	1153.00±227.67	6.59±0.37^{b}
Group 2	120.28±22.44	62.57±7.04	203.57±48.51^{a}	1261.57±217.66	6.23±0.23^{a,b}
Group 3	121.57±17.36	62.85±2.60	227.28±47.78^{a}	1019.85±307.54	6.03±0.22^{a}
Group 4	101.00±7.18	63.71±6.82	201.14±49.41^{a}	979.42±240.52	6.07±0.24^{a}
Group 5	137.14±47.20	60.14±5.17	222.85±47.04^{a}	1253.14±390.16	6.36±0.26^{a,b}
Group 6	99.00±11.26	53.42±7.04	205.28±31.88^{a}	972.71±366.64	6.09±0.23^{a}
P values	0.08	0.22	0.00	0.25	0.00

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b} The same letters in the same column indicatesimilarity between groups, different letters indicate difference between groups($p<0.05$).

control in groups 2, 3 and 6. However, the uricacid level was statistically significantly decreased in all groups when compared to the control; this decrease was more pronounced in FL+BA groups (Groups 3 and 4) ($p<0.05$). When the uricacid level was compared between the groups, Groups 2, 5, 6, and Groups 3, 4 were similar (Table 1).

When the study results were evaluated, although there were changes in AST, ALT and LDH levels in the FL and BA groups compared to the control, there was nostatistically significant difference. However, when comparing the ALP levels between groups, it was statistically significantly lower in all groups compared to the control group ($p<0.05$). Also, total protein level was lower in all groups than the control ($p<0.05$) (Table 2).

Effects of baicalin and flumethrin on lipid peroxidation parameters in liver and kidney tissues

Lipid peroxidation parameter levels (MDA, SOD, NO, GSH-Px and CAT) in liver and kidney tissues are shown in Tables 3 and 4.

According to the present study results (Table 3), the MDA level in the liver tissues increased significantly in the flumethrin-administered toxication group compared to the other groups. Groups 5 and 6 were similar to the control group. Also, the MDA level decreased significantly in the groups that were given baicalin in addition to flumethrin. The SOD activity in the liver tissues was statistically significantly lower in the flumethrin toxication group compared to the other groups. The results of the two groups, in which only baicalin was administered in two different doses, were similar to those of the control. The SOD level in all groups given baicalin was statistically significantly higher than in the toxication group receiving only flumethrin (Group 2). When the results were evaluated in terms of the NO level in the liver tissues, there was a statistically significant increase in the NO level in the group given only flumethrin compared to all other groups. The NO levels of all groups that were given baicalin were similar to the control. The liver GSH-Px enzyme activity was not statistically different in all groups. The CAT activity showed a statistically significant decrease in the flumethrin group (Group 2) compared to the control when comparing groups. The CAT activity was similar to the control group in the groups that were given baicalin (Groups 3, 4, 5, and 6) ($p<0.05$).

In kidney tissue (Table 4), it was ascertained that, when the MDA level was compared between the groups, the MDA level of the group that received only flumethrin (Group 2) showed significantly higher than the control and all other groups. The results of the two groups that were given only baicalin in two different doses (Groups 5 and 6) were similar to the control group's results. In the groups where flumethrin and baicalin were administered together (Groups 3 and 4), the MDA level was lower than in Group 2. The changes in activities of the SOD were not statically crucial in allgroups. According to the data, the NO level in the kidney tissues increased statistically in the flumethrin group compared to all other groups. The NO level was similar to the control in the groups that were given baicalin. The GSH-Px activity decreased significantly in Group 2 compared to all other groups, including control. The results of the rat group in which only baicalin was administered at high doses were similar to the control group. Flumethrin administration in rats significantly decreased the CAT activity

Table 3. Effects of baicalin and flumethrin administration on liver MDA, SOD, NO, GSH-Pxand CAT levels in rats

Groups	MDA (µmol/g)	SOD (U/g protein)	NO (nmol/mg protein)	GSH-Px (nmol/dk/mg protein)	CAT (k/g protein)
Group 1	2.21±0.33 ^{a}	0.056±0.009 ^{a}	2.45±0.27 ^{a}	17.43±5.57	1233.22±165.80 ^{a}
Group 2	3.33±0.47 ^{b}	0.041±0.004 ^{b}	3.30±0.17 ^{b}	13.69±4.47	811.82±127.70 ^{b}
Group 3	2.84±0.31 ^{a,b}	0.048±0.008^{a,b}	2.68±0.33 ^{a}	14.90±4.20	1005.95±193.83^{a,b}
Group 4	2.69±0.55 ^{a,b}	0.047±0.002^{a,b}	2.57±0.30 ^{a}	13.25±4.53	1029.09±281.09^{a,b}
Group 5	2.30±0.35 ^{a}	0.054±0.005 ^{a}	2.58±0.18 ^{a}	15.96±6.61	1126.89±247.49^{a,b}
Group 6	2.39±0.32 ^{a}	0.053±0.008 ^{a}	2.36±0.33 ^{a}	17.71±6.02	1182.63±263.78 ^{a}
P values	0.00	0.00	0.00	0.51	0.01

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b} The same letters in the same column indicate similarity between groups, different letters indicate difference between groups ($p<0.05$).

Table 4. Effects of baicalin and flumethrin administrations on kidney MDA, SOD, NO, GSH-Px and CAT levels in rats

Groups	MDA (µmol/g)	SOD (U/g protein)	NO (nmol/mg protein)	GSH-Px (nmol/dk/mg protein)	CAT (k/g protein)
Group 1	1.36±0.23 ^{a}	0.083±0.006	2.38±0.49^{a,b}	21.22±6.18 ^{a}	229.77±48.03^{a,b}
Group 2	2.11±0.14 ^{c}	0.075±0.002	2.83±0.23 ^{b}	13.28±3.21 ^{b}	187.00±26.03 ^{a}
Group 3	1.71±0.28 ^{b}	0.078±0.003	2.29±0.16 ^{a}	15.01±4.66^{a,b}	211.98±18.43^{a,b}
Group 4	1.75±0.19 ^{b}	0.078±0.008	2.35±0.25 ^{a}	19.00±4.54^{a,b}	219.04±20.96^{a,b}
Group 5	1.35±0.13 ^{a}	0.084±0.005	2.22±0.28 ^{a}	20.80±5.25^{a,b}	228.27±56.24^{a,b}
Group 6	1.32±0.12 ^{a}	0.081±0.008	2.10±0.16 ^{a}	21.61±4.17 ^{a}	267.80±69.17 ^{b}
P values	0.00	0.10	0.00	0.00	0.04

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b,c} The same letters in the same column indicate similarity between groups, different letters indicate difference between groups ($p<0.05$).

in the kidney tissues compared to all other groups, including the control. This enzyme activity in Groups 3, 4, and 5 did not change compared to the control. The group results that received only baicalin at a high level were statistically significantly higher than all groups, including the control ($p<0.05$).

Histopathological evaluation of tissues

Histopathological lesions were depicted on Figures 1 and 2.

As seen in figures (Figure 1 and 2), in the group that was given flumethrin (Group 2), it was noted that there was severe vacuolar degeneration in hepatocytes in liver tissues (Fig1b). As a result of the histopathological evaluation of the kidneys, severe degeneration was observed in the tubulusepithelium (Fig2b). In Group 3 and Group 4, lesions in all tissues regressed (Fig 1c and 2c). It was observed that the degree of recovery in tissues (1d and 2d). No histopathological lesions were found in the groups that were given only baicalin (Group 5 and 6).

DISCUSSION

Flumethrin is an insecticide frequently used in agriculture and in veterinary medicine to combat ectoparasites. In our study, flumethrin toxicity occuredin rats, and baicalin was administered in different doses for 28 days. The aim was to determine lipid peroxidation parameters in liver and kidney

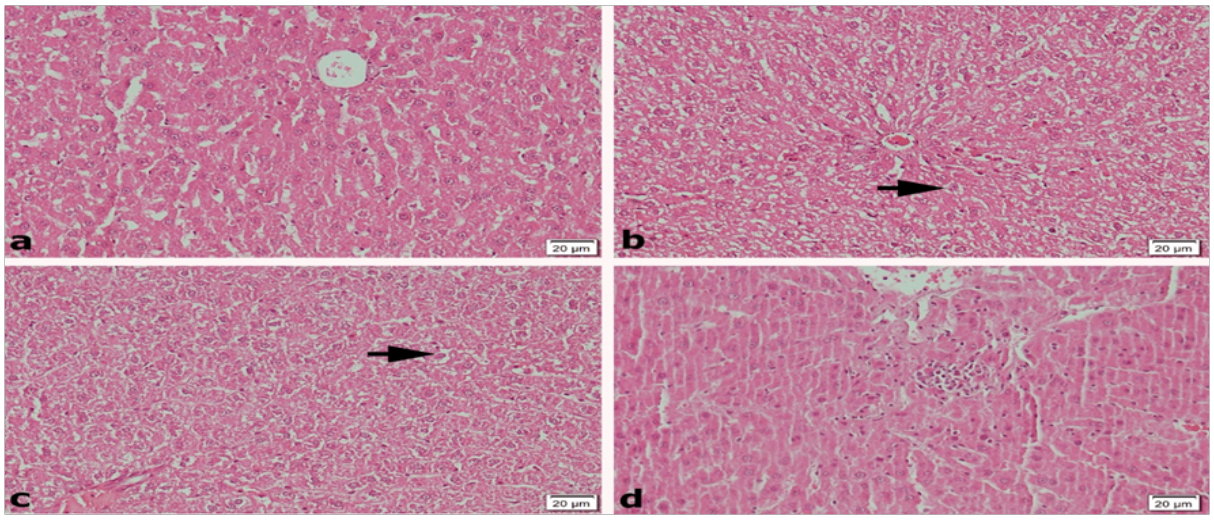

Figure 1: Histopathological evaluation of liver tissue

a) Control liver tissue. H&E, Bar: 20µm
b) Severe degeneration of hepatocytes (arrow). Group 2. H&E, Bar: 20µm
c) Moderate degeneration of hepatocytes (arrow). Group 3, H&E, Bar: 20µm
d) Regressed liver degeneration (arrow). Group 4, H&E, Bar: 20µm

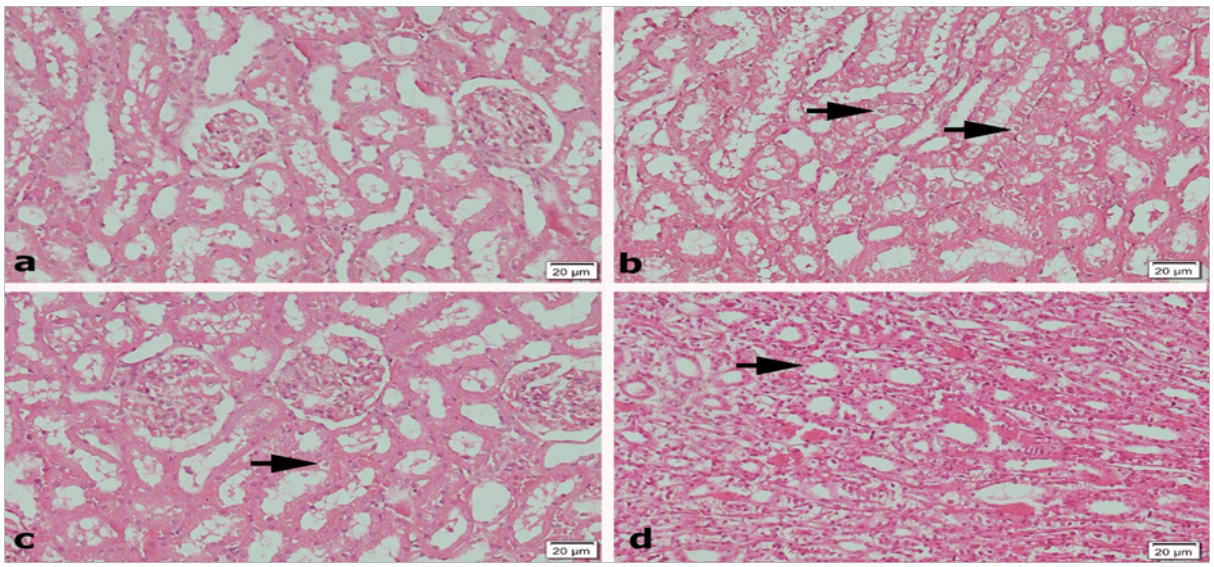

Figure 2: Histopathological evaluation of kidney tissue

a) Control group kidney tissue. H&E, Bar: 20µm
b) Severe degeneration of tubulusepithelium (arrows). Group 2, H&E, Bar: 20µm
c) Mild degeneration of tubulusepithelium (arrow). Group 3, H&E, Bar: 20µm
d) Mild degeneration of tubulusepithelium (arrow). Group 4, H&E, Bar: 20µm

tissues and the biochemical enzyme levels in the blood and evaluate the histopathologica lchanges in liver and kidney tissues.

In the literature review, some studies have been reported about the effects of flumethrin in animals. In a seven-day study performed by Küçükkurt et al. (2010) on the effects of flumethrin in sheep, it was found that there was no significant difference in blood MDA and NO levels, while GSH, CAT and SOD activities decreased.[30] Kanbur et al. (2010) showed that NO and MDA levels in plasma and all tissues increased CAT and SOD activities decreased in all tissues. Also, GSH-Pxenzymeactivity decreased significantly in erythrocytes, while increased in tissues of flumethrin-induced rats.[7] Salama et al. (2019) indicated that MDA level increased, SOD, CAT and GSH activities decreased in brain and liver tissues induced by flumethrin in rat.[10] In another 14-day study about the effects of flumethrin in rats, it was observed that flumethrin caused to increase in MDA level which is an important indicator of lipid peroxidation. Since the production of free radical sincreases with the effect of flumethrin, it is expected that an increase in the level of endogenous antioxidant enzymes (CAT and SOD) involved in cleansing these radicals may be to occurinitially. They reported that to be thereason for the increase in SOD and CAT activities in acute studies.[8] Mishra et al., (2012) revealed that flumethrin increased MDA level, but decreased SOD, and CAT activities in tissue of rat.[9] In the present study, when flumethrin-induced group compare to control group, MDA and NO level sincreased in kidney and liver tissues. On the other hand, CAT level decreased in both kidney and liver tissues, while SOD in the liver and GSH-Px in kidney tissue. Thus, flumethrin toxication caused to significantly an increase in the level of free radicals. The results of our study were consistent with the results of previous studies.

In literatures, it was reported that ALT and AST levels increased in flumethrin-induced toxication.[8,9] In our study, there was no statistically significant difference for AST and ALT levels in serum. However, when comparing the ALP levels between groups, it was determined that there was a statistically significant decrease in all groups compared to the control. Also, flumethrin expose led to a significant decrease in the levels of total protein, cholesterol, BUN, and uric acid in serum in rats ($p < 0.05$).

In a hydrogenperoxide-induced oxidative stress study in rats conducted by Zheng et al. (2014),[31] it was reported that the administration of baicalin decreased the MDA level while it increased the SOD and GSH-Px activities. Jang et al. (2003) revealed that hepatoprotective effects of baicalin on acetaminophen-induced liver damage in mice.[32] Su et al. (2017) demonstrated that baicalin have the all eviation effect to the liver and kidney damage induced-cinnabar in rat.[33] As known that, SOD, CAT, and GSH-Px enzymes form an antioxidant defense against oxidative stress. In the present study, flumethrin administration caused a decrease in SOD enzyme activity in liver tissue, GSH-Px enzyme activity in kidney tissue, and CAT enzyme activity in both tissues. On the other hand, when baicalin-received groups compare to flumetrin-induced group, these antioxidant enzymes were increased in baicalin-received groups.

The previous studies about flumethrin were examined, but there was not enough literature on histopathological findings. Salama et al. (2019) reported that flumethrin caused to minor histopathological lesions in liver and kidney tissues.[10] When the histopathological findings in our study were examined, the observation of severe degeneration in the liver and kidney tissues was in line with the findings in the literature. It was also observed that the tissue damage regressed in the groups treated with flumethrin and baicalin together.

When the experimental data were evaluated, the present study suggests that flumethrin effected some parameters (ALP, cholesterol, BUN, uricacid and total protein) levels in serum and kidney CAT and GSH-Px, liver CAT and SOD activities. Histopathological evaluation revealed that there were some alterations in tissues, when flumethrin administration. Baicalinaltered some parameters (cholesterol, ALP, total protein, BUN, uricacid), NO and MDA levels; it increased kidney CAT and GSH-Px, liver CAT and SOD activities in flumethrin-induced groups. It was determined that the lesions in tissues regressed in the groups where baicalin was applied in flumethrin-induced rats. Biochemical results were consistent with histopathological results.

CONCLUSION

In conclusion, it was observed that alterations in lipid peroxidation parameters and the histopathology of the tissues resulted from the toxic effects of flumethrin. It was concluded that the application of baicalin contributes to the antioxidant defense system, supports tissue healing by reducing oxidation, and plays a constructive role in reversing the negative effects of flumethrin. Thus, baicalin can alleviateoxidativestress and tissue damage in flumethrin-induced subacute toxication in rats. The findings of this study suggest that baicalin might be used as a pharmacological agent in flumethrin toxications.

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Informed Consent: There are noparticipants in the study other than the authors.

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GAIT- AND BALANCE-RELATED FACTORS AFFECTING PARTICIPATION IN SCHOOL-AGED CHILDREN WITH UNILATERAL CEREBRAL PALSY

TEK TARAFLI SEREBRAL PALSİLİ OKUL ÇAĞINDAKİ ÇOCUKLARDA KATILIMI ETKİLEYEN YÜRÜYÜŞ VE DENGE İLE İLGİLİ FAKTÖRLER

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ABSTRACT

Although gait and balance impairments are prevalent in children with unilateral cerebral palsy (UCP), their effects on participation are not completely elucidated. This study aims to explore factors affecting participation in children with UCP, particularly those related to gait and balance. This descriptive relation-seeker study was completed with 40 children with UCP at Gross Motor Function Classification System (GMFCS) levels I and II (50% female; median age = 11 (7-12)years). "The Gross Motor Function Measure (GMFM-66)", "The Pediatric Balance Scale (PBS)", "The Timed Up and Go test (TUG) and The Functional Mobility Scale (FMS)", and "The BTS G-Walk Spatiotemporal Gait Analysis System" were used to evaluate the gross motor function, balance, functional mobility, and quantitative gait parameters, respectively. "The Canadian Occupational Performance Measure (COPM)" was employed to evaluate participation. Variables affecting the COPM scores were analyzed by multivariate regression analysis. The factors affecting the COPM-performance score were cadence (B = 79.859, p = 0.001) and FMS (B = 0.352, p<0.001). These variables explained about 45% of the variation in the COPM-performance score (R^2adj = 0.445). The factors affecting the COPM-satisfaction score were cadence (B = 0.188, p=0.044) and stride length of the more affected side (B = 0.137, p=0.008), which explained 26% of the variation in the COPM-satisfaction score (R^2adj =0 .260).The factors affecting participation in children with UCP were cadence, stride length of the more affected side, and functional mobility. We recommend that rehabilitation specialists consider these factors, as they may be beneficial in designing rehabilitation interventions that effectively promote participation in children with UCP.

Keywords: Activities of daily living, balance, cerebral palsy, gait, participation

ÖZ

Tek taraflı serebral palsili (UCP) çocuklarda yürüme ve denge bozuklukları yaygın olmasına rağmen, bunların katılım üzerindeki etkileri tam olarak aydınlatılamamıştır. Bu çalışma, okul çağındaki UCP'li çocuklarda katılımı etkileyen özellikle yürüyüş ve denge ile ilgili faktörleri araştırmayı amaçlamaktadır. Bu tanımlayıcı ilişki arayıcı çalışma, Kaba Motor Fonksiyon Sınıflandırma Sistemi (GMFCS) seviye I ve II'deki 40 UCP'li çocukla tamamlandı(%50 kız; ortanca yaş = 11 (7-12) yıl). "Kaba Motor Fonksiyon Ölçümü (GMFM-66)", "Pediatrik Denge Ölçeği (PBS)", "Zamanlanmış Kalk ve Yürü Testi (TUG) ve Fonksiyonel Mobilite Skalası (FMS)" ve "BTS G-Walk Spatio-Temporal Yürüyüş Analiz Sistemi" sırasıyla kaba motor fonksiyon, denge, fonksiyonel mobilite ve yürüyüş parametrelerini değerlendirmek için kullanıldı. Katılımı değerlendirmek için "Kanada Mesleki Performans Ölçümü (COPM)" kullanıldı. COPM puanlarını etkileyen değişkenler çok değişkenli regresyon analizi ile incelendi.COPM-performans puanını etkileyen faktörler kadans (B=79.859, p=0.001) ve FMS (B=0.352, p<0.001) idi. Bu değişkenler COPM-performans puanındaki değişimin yaklaşık %45'ini açıkladı (R^2adj=0.445). COPM-memnuniyet puanını etkileyen faktörler ise kadans (B=0.188, p=0.044) ve daha fazla etkilenen tarafın adım uzunluğu (B=0.137, p=0.008) idi; bu değişkenler ise COPM-memnuniyet puanının da ki değişimin %26'sını açıkladı (R^2adj=0.260). UCP'li çocuklarda katılımı etkileyen faktörler kadans, daha fazla etkilenen tarafın adım uzunluğu ve fonksiyonel mobilite idi. UCP'li çocukların katılımını etkili bir şekilde destekleyen rehabilitasyon müdahalelerinin tasarlanmasında yararlı olabileceği için rehabilitasyon uzmanlarının bu faktörleri dikkate almalarını öneriyoruz.

Anahtar kelimeler: Günlük yaşam aktiviteleri, denge, serebral palsi, yürüyüş, katılım

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INTRODUCTION

Affecting 2.11 in every 1000 children in high-income countries, cerebral palsy (CP) is a neuro developmental disorder resulting from non-progressive immature brain impairments and is widely recognized as the most prominent motor disability in children.[1-2] Unilateral CP (UCP), the most prevalent type of CP, often arises from hemi-brain atrophy, periventricular lesions, middle cerebral artery infarction, and brain malformations that disrupt the integrity of motor areas. The resulting motor disorders are largely lateralized to one side affecting both upper and lower extremity function.[3] The disorders in body structure and function (such as muscle weakness, spasticity, and reduced selective voluntary control) encountered in UCP may lead to gait and balance impairments.[4-5] Although most children with UCP can walk without assistance, gait and balance impairments can affect activities of daily living, engagement in sports and leisure time activities, quality of life, and social interactions in this population.[6-7] Compared to their typically developing peers, children with CP experience physical and social difficulties that occur in different ways throughout their lives, and therefore their participation is more restricted.[8]

Participation is a relatively new concept in rehabilitation science terminology and is defined in the scope of the International Classification of Functioning, Disability, and Health (ICF) framework provided by the World Health Organization.[9] According to ICF, participation is described as involvement in life situations and daily activities.[10] Promoting the participation in children with CP is accepted as the ultimate goal of rehabilitation specialists.[11] Thus, understanding the negative or positive contributing factors can help to design rehabilitation interventions that effectively promote participation in children with CP. It was noted that age, gender, motor functions, interests and preferences, physical and social structure of the environment, parental attitude, socioeconomic status, and education level were associated with the participation of children with CP.[10] However, to our knowledge, no study deals with the effect of balance and gait parameters on participation in children with UCP. Given that gait and balance impairments are prevalent in children with UCP, it may be valuable to explore the effects of these impairments on participation for guiding the rehabilitation process. Hence, the aim of this study is to explore the factors affecting participation in children with UCP, particularly those associated with gait and balance.

Study questions

1. What are the gait-related factors affecting participation in school-aged children with UCP?
2. What are the balance-related factors affecting participation in school-aged children with UCP?
3. Are gross motor function and functional mobility factors affecting participation in school-age children with UCP?

MATERIALS AND METHODS

This descriptive relation-seeker study was conducted in the Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Lokman Hekim University. The study protocol was accepted by the Lokman Hekim University Scientific Research Ethics Committee. All children and their parents were informed about the study, and an informed consent form was signed.All procedures of the study were carried out in accordance with the Declaration of Helsinki.

Participants

A convenience clinical sample of children with CP and their parents who were admitted to the Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Lokman Hekim University in Ankara, Türkiye was prospectively included. The Inclusion criteria were (i) having been confirmed with UCP by a pediatric neurologist, (ii) being aged 6 to 12 years, (iii) having Gross Motor Function Classification System (GMFCS) level was I-II, and (iv) having no cooperation problems that may prevent communication. The exclusion criteria were (i) having any previous musculoskeletal surgeries at the lower extremities and (ii) having any pharmacological activity or injection that would inhibit spasticity in the last 6 months. The current study was completed with a total of 40 children with UCP. Sample size and post-hoc power analysis were performed with G*Power (version 3.1.9 Universität Düsseldorf, Düsseldorf, Germany).[12] Since there is no similar study, the effect size of the multiple linear regression, which will investigate the effect of independent variables on COPM-performance and COPM-satisfaction scores, was aimed to be large. Based on the effect size $|f^2| = 0.35$, number of predictors = 2, $\alpha = 0.05$, and power $(1-\beta) = 0.90$, the sample size was calculated as 40. The post-hoc power analysis was performed after the study, and it was found to be 99.9% and 90.7% for the regression models with a statistical significance of $\alpha = 0.05$, $R^2adj = 0.445$ and 0.260, number of predictors = 2, and sample size = 40.

Data Collection Tools

Face-to-face interviews were conducted to obtain research data between June 2023 and September 2023. "The Gross Motor Function Measure (GMFM-66)", "The Pediatric Balance Scale (PBS)", "The Timed Up and Go test (TUG) and The Functional Mobility Scale (FMS)" and "The BTS G-Walk Spatiotemporal Gait Analysis System" were employed to evaluate the gross motor function, balance, functional mobility, and quantitative gait parameters, respectively. "The Canadian Occupational Performance Measure (COPM)" was employed to evaluate participation.

GMFM-66 was used to evaluate the gross motor functions of children with UCP. It is a valid, reliable, and sensitive instrument performed in children with CP to evaluate five dimensions of gross motor function: (A) lying and rolling, (B) sitting, (C) crawling and kneeling, (D) standing, and (E) walking, running and jumping. In this study, only the D and E dimensions were used in accordance with the functional level of children with UCP at GMFCS I and II levels.[13]

PBS was employed to evaluate the balance of children with UCP. It, which is frequently used as a valid and reliable scale in children with CP, contains items for the static and anticipatory balance. It involves 14 items, and each item is scored between 0 and 4; the highest possible score is 56.[14] Erden et al. translated the scale into Turkish and demonstrated its validity (concurrent validity: $r = 0.692$ and $p < 0.001$) and reliability (ICC for interobserver agreement = 0.915; ICC for intraobserver

agreement = 0.927; Cronbach's alpha = 0.857) in evaluating balance in children.[15]

TUG and FMS were used to evaluate the functional mobility of children with UCP. The TUG is a valid and reliable test that measures distinct features including gait velocity, functional mobility, postural control, and balance. It was repeated three times, and these three values were averaged in the analysis.[16] The FMS is a valid and reliable tool for evaluating functional mobility in children with CP, regarding the use of assistive devices at 3 different distances (500 meters-community, 50 meters-school, and 5 meters-indoor). FMS scores of children with UCP were recorded by asking their parents.[17]

BTS G-Walk Spatio-Temporal Gait Analysis System was employed for evaluating the gait parameters of children with UCP. In this system, the data collected by the sensor fixed at the child's L5-S1 level is transferred to a computer via Bluetooth signals. It, which enables gait analysis by collecting 3D kinematic data, provides for a comparison of the right and left lower extremities. The children with UCP were instructed to walk three times in a 10-meter indoor area, and the average of the three measures was taken into account for statistical analysis.[18]

The participation of children with UCP was evaluated by COPM. It is an individual-centered tool for identifying participation restrictions and prioritizing these restrictions in occupational performance areas.[19] In the adapted version of COPM for children, parents identify their child's 5 most important occupational problems without any intervention by the evaluator and score their child's performance and satisfaction with that performance for each problem on a scale of 0-10. Higher scores demonstrate higher performance and satisfaction.[20]

Statistical Analysis

All statistical analysis was conducted using the IBM SPSS Statistics for Windows v26.0 (SPSS Inc., Chicago, USA). The normal distribution of continuous variables was assessed with visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk tests), and all variables except age and BMI were found to be normally distributed.The association between dichotomous variables and continuous variables was examined with the "Point-Biserial Correlation Coefficient", and the association between continuous variables was examined with the "Spearman or Pearson Correlation Coefficient", as appropriate.[21] Correlation coefficients between 0.05–0.30 indicated a low correlation, 0.30–0.40 indicated a low-to-moderate correlation, 0.40–0.60 indicated a moderate correlation, 0.60–0.70 indicated a good correlation, 0.70–0.75 indicated a strong correlation and 0.75–1.00 indicated an excellent correlation.[22] "Multiple Linear Regression Analysis" was performed to identify the factors affecting COPM-performance and COPM-satisfaction scores using the possible variables determined in previous analyses. Before the analysis, it was justified that the assumptions (independence of observations, linear relationship between independent variables and dependent variable, homosced asticity, normally distributed residuals) were met. The factors showing a significant correlation with the COPM-performance and COPM-satisfaction scores with a coefficient above 0.30 were examined in terms of multicollinearity, and only one clinically significant parameter showing multicollinearity (correlation coefficient >0.80) was included in the models. The models' fit was evaluated with appropriate goodness-of-fit and residual statistics (adjusted R^2, residuals vs. fitted plot, and Q-Q plot, residuals vs. predictor plot). A p-value less than 0.05 was determined as an indicator of statistical significance.[21]

RESULTS

The study comprised 40 children with UCP with a median age of 11 (7-12) years, of whom 20 (50%) were female. The mean scores for the PBBS, GMFM-66/D,GMFM-66/E, COPM-performance, and COPM-satisfaction were 48.48±5.04, 48.37±6.37, 12.02±2.18, 22.4±8.84, and 23.15±10.42, respectively. Additional details about the sociodemographic and clinical characteristics of the children are provided in Table 1.

Gender, more affected side, and GMFCS level were not significantly associated with COPM-performance and COPM-satisfaction scores($p>0.05$).COPM-performance score had low-to-moderate associations with FMS ($r=0.331$, $p<0.001$) and pelvic tilt symmetry ($r=0.363$, $p=0.037$), as well as moderate associations with cadence ($r=0.578$, $p<0.001$), gait cycle duration (LAS) ($r=-0.608$, $p<0.001$), and gait cycle duration (MAS) ($r=-0.417$, $p=0.007$). However, there was no association of COPM-performances core with PBBS, TUG, GMFM-66/D, GMFM-66/E, and other gait parameters ($p> 0.05$) (Table 2).

COPM-satisfaction score had low-to-moderate associations with cadence ($r=0.382$, $p=0.015$),gait cycle duration (LAS) ($r=-0.339$, $p=0.033$), and stride length (LAS) ($r=0.348$, $p=0.028$), as well as moderate association with stride length (MAS) ($r=0.464$, $p=0.003$). However, there was no association of COPM-satisfaction score with PBBS, TUG,FMS, GMFM-66/D, GMFM-66/E, and other gait parameters ($p>0.05$) (Table 2).

At least one of the independent variables in the regression models was found to be a significant predictor (factor) and the models were generally significant (COPM-performance: $F(2.39)=16.647$ and $p<0.001$, COPM-satisfaction: $F(2.39)= 7.846$ and $p=0.001$). The cadence ($B=0,327$, $p<0.001$) and FMS($B=6,599$, $p=0.003$) had significant positive effects onthe COPM-performance score (model 1). They accounted for about 45% of the variance in the COPM-performance score ($R^2_{adj}=0.445$). The cadence ($B=0.188$, $p=0.044$) and stride length (LAS)($B=0.137$, $p=0.008$) had significant positive effects on the COPM-satisfaction score (model 2). They accounted for 26% of the variance in the COPM -satisfaction score($R^2_{adj}=0.260$)(Table 3).

DISCUSSION

In the current study, we studied the gait- and balance-related factors affecting participation in children with UCP. The findings revealed that cadence and functional mobility were significant factors affecting participation performance, while cadence and stride length of the more affected side were significant factors affecting participation satisfaction.

To our knowledge, there exists no study dealing with the effect of gait parameters on participation. Thus, the

Table 1. The sociodemographic and clinical characteristics of the children with UCP (n=40)

Age (years)	11(7-12)
BMI (kg/m^2)	19.11 (17.33-21.33)
PBBS	48.48±5.04
TUG	7.49±2.14
FMS	5.43±0.5
GMFM-66/D (standing)	48.37±6.37
GMFM-66/E (walking, running, jumping)	12.02±2.18
Gait Parameters	
Cadence (step/min)	113.92±16.35
Gait Velocity (m/s)	1.18±0.26
Gait Cycle Duration (s)	
LAS	1.11±0.19
MAS	1.12±0.17
Stride Length (Min)	
LAS	1.19±0.23
MAS	1.2±0.22
Stride Lenght (%)	
LAS	96.37±32.8
MAS	99.04±30.35
Step Lenght (%)	
LAS	48.57±3.51
MAS	50.99±3.64
Stance Phase (%)	
LAS	61.69±3.07
MAS	59.5±3.91
Swing Phase (%)	
LAS	38.46±3.22
MAS	50.14±64.14
First Double Support Phase (%)	
LAS	10.89±2.21
MAS	10.43±2.47
Single Support Phase (%)	
LAS	39.74±3.71
MAS	38.15±3.01
Gait Symmetry	83±11.67
Pelvic Tilt Symmetry	33.59±26.71
Pelvic Obliquity Symmetry	84.13±16.24
Pelvic Rotation Symmetry	87.79±16.85
COPM-performance	22.4±8.84
COPM-satisfaction	23.15±10.42
	n (%)
Gender	
Female	20 (50)
Male	20 (50)
More Affected Side	
Right	24 (60)
Left	16 (40)
GMFCS Levels	
Level I	18 (45)
Level II	22 (55)

Values are given as X±SD or median (25th/75th centile). X, mean; SD, Standard Deviation; BMI, Body Mass Index; GMFCS, Gross Motor Function Classification System; PBBS, Pediatric Berg Balance Scale; TUG, Timed Up and Go Test; FMS, Functional Mobility Scale; GMFM-66, Gross Motor Function Scale Measure; COPM, Canadian Occupational Performance Measure; LAS, Less Affected Side; MAS, More Affected Side.

current study is the first to show that cadence and stride length of the more affected side affect participation in children with CP. Bourgeois et al. reported children with CP had reduced spatiotemporal gait parameters including cadence and stride length, which may seriously predispose them toward falls.[23] These findings imply that cadence and stride length may affect participation by causing the child with CP to fall during activities of daily living. The current study showed that gait parameters affect not only participation performance but also participation satisfaction. This finding, which reveals the perception of children with CP towards their daily living, has clinical significance for rehabilitation specialists. Thus, we suggest that improving the cadence and stride length of the more affected side is a key clinical goal in the rehabilitation of children with UCP where the ultimate aim is to promote participation. On the other hand, the absence of an effect of gait parameters on participation, with the exception of cadence and stride length, may be attribut-

Table 2. Associations of the COPM scores with other variables

			COPM-performance	COPM-satisfaction
Gender		**r**	0.132	-0.117
		p	0.418	0.474
More Affected Side		**r**	0.068	0.062
		p	0.678	0.702
GMFCS Level		**r**	-0.154	0.272
		p	0.342	0.089
PBBS		**r**	0.306	0.123
		p	0.055	0.449
Gait Parameters				
Cadence		**r**	0.578	0.382
		p	**<0.001***	**0.015***
Gait Cycle Duration	LAS	**r**	-0.608	-0.339
		p	**<0.001***	**0.033***
	MAS	**r**	-0.417	-0.277
		p	**0.007***	0.083
Stride Lenght (%)	LAS	**r**	0.037	0.348
		p	0.823	**0.028***
	MAS	**r**	0.127	0.464
		p	0.434	**0.003***
Pelvic Tilt Symmetry		**r**	0.363	-0.052
		p	**0.021***	0.752
TUG		**r**	0.301	0.121
		p	0.059	0.459
FMS		**r**	0.331	-0.096
		p	**0.037***	0.555
GMFM-66/D		**r**	0.154	0.126
		p	0.342	0.438
GMFM-66/E		**r**	0.193	-0.031
		p	0.234	0.851

*p<0.05; r, correlation coefficient; Gross Motor Function Classification System; PBBS, Pediatric Berg Balance Scale; TUG, Timed Up and Go Test ; FMS, Functional Moility Scale; GMFM-66, Gross Motor Function Scale Measure; COPM, Canadian Occupational Performance Measure; LAS, Less Affected Side; MAS, More Affected Side.

Table 3. Multiple linear regression analysis results of the factors affecting COPM scores

	B	95% CI	t	p	VIF
Model 1					
Constant	-50.641	-79.173/-22.109	-3.596	**0.001***	-
FMS	6.599	2.322/ 10.877	3.126	**0.003***	1.005
Cadence	0.327	0.196/ 0.458	5.057	**<0.001***	1.005
Model 2					
Constant	-11.820	-32.932/9.293	-1.134	0.264	-
Cadence	0.188	0.005/0.370	2.086	**0.044***	1.05
Stride Lenght of MAS	0.137	0.039/0.235	2.828	**0.008***	1.05

*p<0.05; B, Un standardized coefficient; CI, Confidence Interval; VIF, Variance Inflation Factor; MAS, More Affected Side; COPM, Canadian Occupational Performance Measure.
Model 1: The dependent variable is COPM-performance, n=40, R^2_{adj}=0.445, Model: Backward Method.
Model 2: The dependent variable is COPM-satisfaction, n=40, R^2_{adj}=0.260, Model: Backward Method.

able to the fact that our study population included GMFCS level I-II children with out severe gait disorders.

The present study revealed that functional mobility affects participation in school-age children with UCP. Furtoda et al. stated that functional mobility had a strong association with the school participation of children and youths with CP.[24] Schenker et al. noted that children with CP at GMFCS I and II levels had higher participation in regular school classes or special classes compared to children at GMFCS levels III.[25]Since they learn new tasks, establish friend ships, develop social roles, and their social environments rapidly broaden during the school-age period, school is one of the most essential participation areas for children with CP. There fore, rehabilitation approaches that focus on increasing functional mobility and environmental adjustments to address mobility barriers both with in and outside of the school may promote participation in children with UCP.

In this study, gender and age did not have a significant

effect on participation in school-age children with UCP. Similar to our study, Seyhan-Bıyık et al. reported that gender is not effective in participation in children with CP.[26] In contrast to our study, Reedman et al. stated that there is a significant association between age and participation in children with CP at the GMFCS I-III levels and participation score decreases as age increases. They speculated that decreased levels of physical activity and parental control, as well as children's preference for sedentary leisure time activities as age increases, may be responsible for this association.[27] The possible reasons for why there was no significant association between age and participation in our study are that children with CP at the GMFCS I-II levels have fewer participation restrictions and better ambulatory levels than children with CP at the GMFCS III level.[28] From this viewpoint, it can be inferred that children with CP at the GMFCS I-II levels could maintain their participation despite their increasing age.

This study demonstrated that balance and gross motor function have no significant effect on participation in school-age children with UCP. The PBS is used to assess balance, and scores between 41 and 56 are interpreted as good balance.[29] We consider that balance is not a significant factor in participation because the children with CP at the GMFCS I-II levels in our study have good balance, with an average PBBS score of 48. Vila-Nova et al. stated that compared to peers without motor disorders, children with CP at GMFCS II-V participate in team sports, individual physical activities, and cycling less frequently.However, they reported no differences between children with CP in GMFCS I and peers without motor impairments in terms of physical activity participation.[30] This finding implies that gross motor function is associated with physical activity participation only in children with CP at higher levels of GMFCS. Furthermore, it was noted that children with CP at the GMFCS I-II level are less restricted in their physical activity participation compared to children with CP at other GMFCS levels.[27] Considering that our study sample consisted of children with UCP at GMFCS I -II level, we infer that children with CP at lower levels of GMFCS have a mild motor impairment and that this motor impairment does not prevent participation.

The present study had several limitations. First, the convenience sampling method was used to include children from Ankara province. Second, our study sample consisted of school-age children with UCP at the GMFCS I-II level. These two limitations may weaken the generalizability of the findings and the representativeness of the sample. Future studies should use random sampling methods and include participants in other CP types, age groups, and GMFCS levels. Third, only cross-sectional associations and effects could be examined due to the design of our study. Nevertheless, our study may provide preliminary data and shed light on further longitudinal or experimental studies.

CONCLUSION

This study shows that the factors affecting participation in children with UCP were cadence, stride length of the most affected side, and functional mobility. We believe that awareness of the effect of these factors on participation may be crucial in guiding participation-oriented rehabilitation interventions.

Ethics Committee Approval: This study was approved by the Ethics Committee of Lokman Hekim University (June 13, 2023, Number: 2023/087).
Informed Consent: Written and/or verbal consent was obtained from children and their parents participating in the study.
Peer-review: Externally peer-reviewed.
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EFFECTS OF ALBUMIN ADMINISTRATION ON CYTOCHROME C-1 (CYC1) IN ISCHEMIA-REPERFUSION DAMAGED RAT OVARY

İSKEMİ-REPERFÜZYON HASARLI RAT OVARYUMUNDA ALBÜMİN UYGULAMASININ SITOKROM C-1 (CYC1) ÜZERINE ETKİLERİ

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ABSTRACT

This study aimed to examine the effects of albumin administration on ischemia-reperfusion in the rat ovary by using biochemical, histological, and immunohistochemical methods. Thirty-two *Wistar albino* rats were used in the study, and they were divided into 4 groups: control, albumin, placebo, and ischemia-reperfusion. Healthy ovaries were taken from the first group. In the other three groups, 2-hour ischemia and 2-hour reperfusion were applied to the bilateral ovaries. In the albumin group, intraperitoneal albumin (2.5 g/kg, 20% human albumin) was administered 30 minutes before reperfusion, and in the placebo group, the same volume of intraperitoneal saline was administered instead of albumin 30 minutes before reperfusion. Ovarian damage scores, cytochrome C-1 immunoreactivity, total oxidant status, total antioxidant status, and oxidative stress index levels were evaluated. In the statistical analysis performed between the groups, it was seen that the results of the control group were significantly lower than the ischemia-reperfusion group in terms of total oxidant status values ($p=0.001$), and the results of the ischemia-reperfusion group were significantly higher than the control and albumin groups in terms of oxidative stress index values ($p<0.001$ and $p=0.004$, respectively). In histological examinations, the total damage score obtained by evaluating follicular degeneration, edema, vascular congestion, and hemorrhage was found to be significantly higher in the ischemia-reperfusion group than in the control group ($p=0.003$). According to the immunohistochemical examination results, cytochrome C-1 immunoreactivity in the ischemia-reperfusion group was significantly stronger than the control and albumin groups ($p<0.001$). We think that albumin administration reduces cytochrome C-1, reactive oxygen species, and oxidative stress levels, therefore it will play a helpful role in the ischemia-reperfusion treatment process.

Keywords: Cytochrome C-1, human serum albumin, immunohistochemistry, ischemia-reperfusion, Ovary.

ÖZ

Bu çalışma, albumin uygulamasının rat ovaryumunda iskemi-reperfüzyon üzerine etkilerini biyokimyasal, histolojik ve immune histokimyasal yöntemlerle incelemeyi amaçladı. Çalışmada 32 adet *Wistar albino* rat kullanıldı. Hayvanlar 4 gruba ayrıldı: kontrol, albümin, placebo ve iskemi-reperfüzyon. Birinci gruptan sağlıklı overler alındı. Diğer 3 grupta overlere bilateral 2 saatlik iskemi ve 2 saatlik reperfüzyon uygulandı. Albümin grubuna reperfüzyondan 30 dakika önce intraperitoneal albumin (2.5g/kg, %20 human albumin), placebo grubuna reperfüzyondan 30 dakika önce albumin yerine aynı hacimde intraperitoneal salin verildi. Yumurtalık hasar skorları, Sitokrom C-1 immüno reaktivitesi, toplam oksidan durumu, toplam antioksidan durumu ve oksidatif stress indeksi değerleri değerlendirildi. Gruplar arasında yapılan istatistiksel analizlerde toplam oksidan durumu değerleri açısından control grubu sonuçları iskemi-reperfüzyon grubuna gore belirgin olarak düşük olduğu ($p=0.001$) ve oksidatif stress indeksi değerleri açısından ise iskemi-reperfüzyon grubu sonuçlarının control ve albumin gruplarına gore anlamlı olarak yüksek olduğu görüldü ($p<0.001$ ve $p=0.004$, sırasıyla). Histolojik incelemelerde folikül dejenerasyonu, ödem, damar tıkanıklığı ve hemoraji değerlendirilerek elde edilen toplam hasar puanı IR grubunda control grubuna gore anlamlı olarak yüksek bulundu ($p=0.003$). İmmüno histokimyasal inceleme sonuçlarına gore iskemi-reperfüzyon grubundaki sitokrom C-1 immün reaktivitesinin control ve albumin gruplarına gore anlamlı derecede daha güçlüydü ($p<0.001$). Albümin uygulamasının sitokrom C-1, oksijen radikalleri ve oksidatif stress düzeylerini düşürdüğünü, bu nedenlei skemi-reperfüzyon tedavi sürecinde yardımcı bir rol oynayacağını düşünüyoruz.

Anahtar kelimeler: Sitokrom C-1, insan serum albümini, immünohistokimya, iskemi-reperfüzyon, ovaryum, .

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INTRODUCTION

Ovarian torsion is the sixth most frequent gynecological emergency. The therapy is to execute detorsion to restore blood flow.[1-3]Delayed diagnosis and treatment of ovarian torsion in women results in necrosis and organ loss in the ovaries.[4] Cell damage is caused by reactive oxygen species (ROS) generated during torsion-induced ischemia.[5] The ROS is one of the major causes of tissue damage.[6] Reperfusion is required to repair ischemia-induced tissue damage and to eliminate harmful metabolites from the organ. However, it is well known that reperfusion causes further damage.[7,8] Detorsion causes the movement of polymorph nuclear leukocytes and platelets toward ischemic tissue, follicular cell degeneration in the ovaries, and interstitial and intrafollicular hemorrhages. Furthermore, this condition accelerates the production of ROS.[1,2]

One of the most essential components that triggers apoptosis is Cytochrome C (Cyt-C), which initiates apoptosis by moving from the mitochondria to the cytoplasm. CYC1, which is also known as isoform-1 cytochrome C, is the homolog of cytochrome C1. Because of this reason, CYC1 is a marker for the existence of the apoptotic pathway.[9] ROS, which is created in excess as a result of ischemia-reperfusion (IR), disrupts mitochondrial functioning.[10] The release of CYC-1 from the mitochondria into the cytoplasm is increased when the mitochondrial functioning is disrupted.[9]

Albumin, which also possesses antioxidant capabilities, is the most abundant protein in the plasma and is responsible for the majority of the ROS capture. Albumin also protects against damage caused by lipid peroxidation and peroxyl radicals.[11] In addition, it reduces reperfusion-induced inflammatory response by improving microcirculation and preventing organ dysfunction.[12]

Here, we aimed to examine the effects of albumin administration on ischemia-reperfusion in the rat ovary by using biochemical, histological, and immunohistochemical (IHC) techniques.

MATERIALS AND METHODS

Animals

This study was imposed in accordance with the "Care and Use of Laboratory Animals Guidelines" in the Animal Experiments Laboratory of Kafkas University. The permission for the experiment was given from the Animal Experiments Local Ethics Committee of Kafkas University (decision date/numbered; 23-09-2021 / 2021-138). For the study, 32 female *Wistar albino* rats (8-12 weeks aged, weighing 180-260 g) were utilized. They were fed ad libitum and kept in a room that had a 12-hour day-night cycle and 22 ± 2.

Groups

In this study, thirty-two rats were randomly and equally divided into four groups.

Control group: After anesthesia, healthy ovarian tissues were bilaterally excised.

Albumin group: After anesthesia, 2-hour ischemia and 2 -hour reperfusion were done. 30 minutes before the initiation of reperfusion, 2.5 g/kg 20% human albumin (12.5 ml/kg) was injected intraperitoneally.[13] The ovarian tissues were extracted bilaterally at the end of the reperfusion period.

Placebo group: After anesthesia, 2-hour ischemia and 2-hour reperfusion were done. 30 minutes before the initiation of reperfusion, 12.5 ml/kg saline was injected intraperitoneal. The ovarian tissues were extracted bilaterally at the end of the reperfusion period.

IR group: After anesthesia, 2-hour ischemia and 2-hour reperfusion were done. The ovarian tissues were extracted bilaterally at the end of the reperfusion period.

Anesthesia

According to the body weight, 10 mg/kg xylazine (Vetaxyl®, Vet-Agro) and 90 mg/kg ketamine (Keta-Control®, Doa Pharmaceuticals) were administrated by intramuscular injection for anesthesia.

Surgical method

After anesthesia, all rats were found supine, and a 2 cm abdominal incision was performed after the surgical site was shaved and sterilized. The abdomen was closed after the adnexa including the tuba and ovarian arteries was ligatured with a 3/0 silk suture.[14] The abdomen was opened again, the ligature around the adnexa was removed for reperfusion, and the abdomen was closed again. After reperfusion, the abdomen was opened and tissue and blood samples were taken.

Biochemical analysis

The blood serum was used to test albumin, calcium, total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI). TOS and TAS were determined using Erel's automated colorimetric technique (Rel Assay Diagnostics®, Mega Tıp, Türkiye).[6] TOS values are reported in μmol H_2O_2Eq/L units. TAS levels are reported in mmol Trolox Eq/L. OSI is the ratio of TOS to TAS in μmol [(TOS/(TAS*1000))*100], and it is an indicator of oxidative stress levels. Albumin and calcium were determined using a colorimetric technique (Otto Scientific®, Mega Tıp, Türkiye) with a spectrophotometer. Albumin levels are reported in g/dL. Calcium levels are reported in mg/dL.

Histological analysis

After follow-up procedures, the ovarian tissues were preserved in 10% formalin and embedded in paraffin blocks.[3] Serial sections at 5 μm thickness were taken from these blocks by using a microtome (Leica RM2125RTS).Haematoxylin-eosin (H&E) was applied and taken photos by using a light microscope (Olympus Bx53, Tokyo, Japan). Two slides of every subject and five- fields in each slide were examined and scored at 10x magnification to determine the ovaries' tissue damage levels and scored, which were scored by considering follicular cell degeneration, hemorrhage, vascular congestion, and edema (0=none, 1=weak, 2=moderate, 3=strong).The total score of tissue injury was calculated by adding these scores.[1]The follicle degeneration was evaluated in the primordial, primary, secondary, and graff follicles.

Avidin-biotin-peroxidase complex (ABC) staining was used for IHC staining. We employed a 1:100 dilution of a monoclonal CYC1 primary antibody (Elabscience, E-AB-40271). CYC1 IHC was applied and taken photos by using a light microscope (Olympus Bx53, Tokyo, Japan). Two slides from each subject and five fields on each slide were examined at 10x magnification and scored to determine the intensity of CYC1 immunoreactivity(0=none, 1=weak, 2=moderate, 3=strong).[3]

Statistical Analysis

The data from our study were analysed using the IBM SPSS Statistical version 25 (IBM®, USA). The means and standard deviations of the datawere calculated. Then, a one-way ANOVA test was used to compare biochemical data between groups. Post-hoc Türkiye test was used for multiple comparisons in one-way ANOVA. Median, minimum and maximum values were determined in histological and immunohistochemical score evaluations. Then, the Kruskal-Wallis test was used for comparisons between groups, and the Mann Whitney-U test was used for pairwise comparisons of groups. In comparisons between groups, statistical significance was accepted as $p<0.05$. In pairwise comparisons of groups, the p value was considered significant at $p\leq0.008$ (p value/number of tests=0.05/6) by applying Bonferroni correction to avoid type 1 error. Since follicle degeneration values of both control and albumin groups were zero, they were excluded from the analysis.

RESULTS

Biochemical findings

The results of biochemical tests are shown in the table (Table 1). TOS values of the control group were significantly lower than those of the placebo and IR groups (p=0.008, p=0.001, respectively). Again, the OSI values of the control group were significantly lower than the placebo and IR groups (p=0.019, p<0.001, respectively). TOS values of the albumin group were significantly lower than the IR group (p=0.018). Again, the OSI values of the albumin group were significantly lower than those of the IR group (p=0.004). Albumin and placebo groups were similar in terms of TOS and OSI scores. Calcium, albumin, and TAS values did not show a statistically significant difference between the groups.

Histological findings

In the control group, hemorrhagic patches and edema were seldom found surrounding the follicles. In the cortex, there was little vascular congestion. The control group showed no evidence of follicle degeneration. In the medulla region, there were minor hemorrhagic patches and vascular congestion (Figure 1, A-B).

Hemorrhagic areas and minor vascular congestion were found in the cortex and medulla regions of the albumin group at a similar level to the placebo group. Edema ranged from moderate to extensive throughout the tissue. The albumin group did not have follicle degeneration (Figure 1, C-D).

The placebo group experienced follicle degeneration. There were somewhat more hemorrhagic spots throughout the tissue than in the control group, and there was modest vascular congestion in the cortical regions. Furthermore, there was mild to severe widespread edema throughout the tissue. The medulla slice showed moderate hemorrhage regions and modest vascular congestion (Figure 1, E-F).

Follicle degeneration was detected in the IR group to a lesser extent. Mild hemorrhagic patches were seen in the cortex and medulla. Throughout the tissue, there was some vascular congestion and moderate edema (Figure 1, G-H).

Histopathological evaluation results are shown in the table (Table 2). There was a statistically significant

Table 1. Comparisons of biochemical findings between groups (mean ± SD).

Groups	Calcium (mg/dL)	Albumin (g/dL)	TAS (mmol/L)	TOS (µmol/L)	OSI
Control	9.32 ± 0.45^{a}	3.42 ± 0.23^{a}	1.60 ± 0.15^{a}	8.46 ± 4.46^{a}	0.52 ± 0.26^{a}
Albumin	9.92 ± 0.65^{a}	3.50 ± 0.15^{a}	1.58 ± 0.20^{a}	11.51 ± 4.25^{ab}	0.74 ± 0.30^{ab}
Placebo	10.07 ± 0.36^{a}	3.31 ± 0.21^{a}	1.53 ± 0.06^{a}	18.89 ± 8.47^{bc}	1.22 ± 0.50^{bc}
IR	9.73 ± 0.72^{a}	3.33 ± 0.29^{a}	1.43 ± 0.51^{a}	20.96 ± 5.64^{c}	1.56 ± 0.59^{c}
p-value*	0.071	0.336	0.639	0.001*	<0.001*

**: p<0,05 (Oneway ANOVA). SD: Standard Deviations.^{a,b,c}: Different superscripts in the same column indicate statistical differences between groups (post-hoc Tukey p<0.05).*

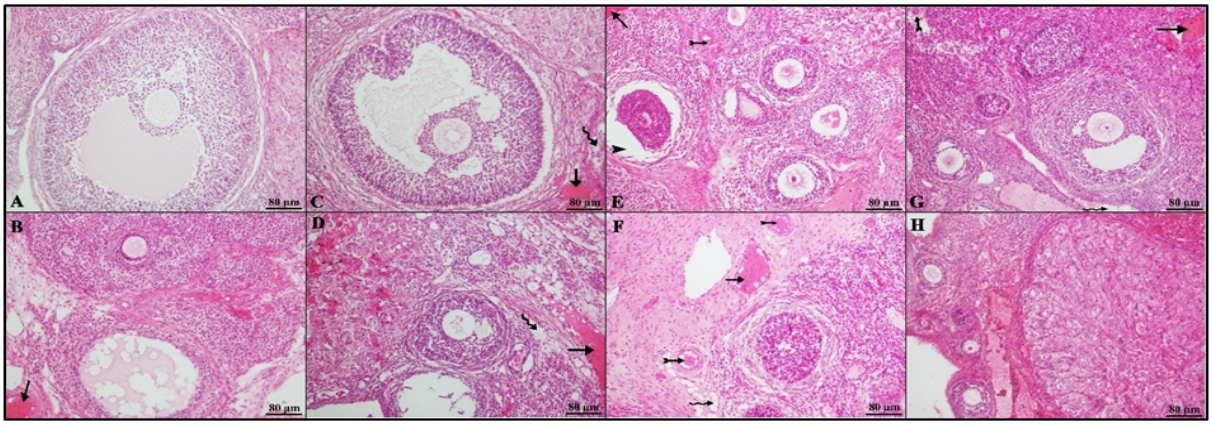

Figure 1.H&E staining, 20x magnification (80µm). **A-B**. Control group,**C-D.** Albumin group, **E-F.**Placebo group, **G-H.** IR group. (Straight arrow: Hemorrhage, Curved arrow: Edema, Arrowhead: Follicular degeneration, Vest arrow: Vascular congestion.)

difference between the IR group and placebo groups in terms of follicular degeneration (p=0.004). The difference in edema scores between the placebo and control groups was statistically significant (p=0.007). There was a statistically significant difference between the control group and the placebo and IR groups in the total scoring (p=0.008, p=0.003, respectively). There was no strong difference between the groups in terms of vascular congestion and hemorrhage.

Immunohistochemical findings

In the control group, no significant CYC1 immuno reactivity was seen in follicle granulosa cells and theca layers. Ovarian connective tissue cells showed partial immune reactivity. However, modest widespread immune reactivity was seen in corpus luteum granulosa lutein cells (Figure 2, A-B).

Weak CYC1 immuno positivity was identified in follicular granulosa cells and theca layers in the albumin group, and weak CYC1 immuno reactivity in ovarian connective tissue. In corpus luteum granulosa lutein cells, immune positivity was shown to be somewhat extensive (Figure 2, C-D).

The Placebo group showed moderate CYC1 positivity in follicular granulosa cells and theca layers. Rare immune reactivity was found in cumulus oophoruses. Ovarian connective tissue cells showed somewhat extensive staining. In contrast, moderate and widespread CYC1 immuno reactivity was seen in corpus luteum granulosa lutein cells (Figure 2, E-F).

In the IR group, follicular granulosa cells and theca layers showed moderate CYC1 immuno reactivity. In ovarian connective tissue cells, immune reactivity ranged from moderate to strong. In the corpus luteum, granulosa lutein cells of the IR group, strong widespread staining was seen (Figure 2, G-H).

CYC1 immunohistochemical examination results are shown in the table (Table 3). In terms of CYC1 immuno reactivity, a statistically important difference was identified between the control group and the other groups (p<0.001 in all). Furthermore, there was a statistically significant difference in CYC1 immuno reactivity results between the albumin group and the IR groups (p=0.003). In terms of CYC1 immuno reactivity, there was no statistical difference between the placebo and IR groups.

Table 2. Comparisons of histopathological findings between groups [median (min – max)].

Groups	Follicle Degeneration	Hemorrhage	Vascular Congestion	Edema	Total Score
Control	0(0–0)	1(0–1)^{a}	0(0–1)^{a}	1(0–1)^{a}	2 (0–3)^{a}
Albumin	0(0–0)	1(1–3)^{a}	0 (0–1)^{a}	1.5(1–3)^{ab}	3(2–5)^{ab}
Placebo	0(0–1)^{a}	1.5(0–3)^{a}	0 (0–1)^{a}	2(1–3)^{b}	3.5(2–5)^{b}
IR	1(0–1)^{b}	1(0–2)^{a}	0.5(0–1)^{a}	1.5(0–2)^{ab}	3.5(2–5)^{b}
p-value*	<0.001*	0.126	0.639	0.034*	0.010*

**: p<0,05 (Kruskal wallis). min: Minimum. max: Maximum. ^{a,b}: Different superscripts in the same column indicate statistical differences between groups (Mann Whitney-u, p≤0.008). Note: The comparison was done between placebo and IR groups for follicle degeneration.*

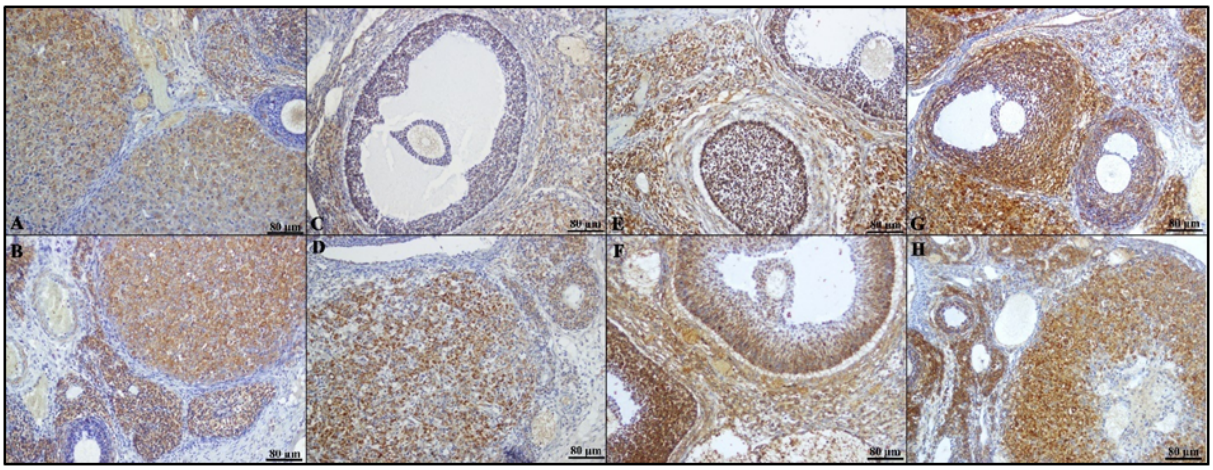

Figure 2. CYC1 IHC staining, 20x magnifications(80μm). **A-B.** Control group, **C-D.** Albumin group,**E-F.** Placebo group,**G-H.** IR group.

Table 3. Comparisons of CYC1 immunoreactivity between groups [median (min – max)].

	Control	Albumin	Placebo	IR	*p-value**
CYC1	1(1–1)^{a}	2(2–2)^{b}	2.5(2–3)^{c}	3 (2–3)^{c}	<0.001*

**: p<0,05 (Kruskal wallis).min: Minimum. max: Maximum.^{a,b,c}: Different superscripts on the same row indicate statistical differences between groups (Mann Whitney-u, p≤0.008).*

DISCUSSION

An experimental bilateral IR model was generated in rat ovaries for this investigation. The impact of intraperitoneal albumin administration on ovarian tissue damage and CYC1 immunoreactivity was studied.

In some experimental IR model investigations, there was no change in serum calcium levels across the groups.[15,16]In our study, there was no significant difference between the groups in terms of serum calcium levels. The comparison of serum calcium levels showed that ovarian IR damage did not produce alterations in serum calcium levels between groups.

Some articles in which it was constructed an experimental ovarian IR model showed that the greatest TOS levels were in IR groups.[2,17,18] In the experimental IR model studies in the ovaries, it was found that TOS levels in the IR groups were greater than those in the control groups.[14,19-21] In this investigation, there was a significant difference in terms of TOS levels between the groups. TOS levels rose considerably in the IR group (20.96±5.64 μmol/L) and placebo group (18.89±8.47 μmol/L) compared to the control group (8.46±4.46 μmol/L). Furthermore, the TOS levels in the IR group increased considerably as compared to the albumin group (11.51±4.25 μmol/L). TOS levels in the control and albumin groups revealed similar findings.

In other studies, it was discovered the lowest TAS levels in IR groups in experimental ovarian IR model investigations.[2,14,17-19,21] In the present study, there was no powerful difference between the groups in terms of TAS levels. Despite this, it was established that the IR group had the lowest TAS levels in this study.

Studies on the experimental ovarian IR model stated that the highest OSI levels were in the IR groups.[17,18] In some studies, they reported that the OSI level in the IR group was higher than that of the control group.[14,19-21] In our study, a statistical difference in OSI levels was found between the groups. OSI levels showed a significant increase in the placebo group (1.22±0.50) and IR group (1.32±0.42) compared to the control group (0.61±0.34). In addition, the OSI levels of the IR group also increased significantly compared to the albumin group (0.74±0.30). OSI levels were similar in the control and albumin groups.

Although the highest serum albumin values were seen in the albumin group, there was no visible statistical difference in serum albumin levels between the groups. Although serum albumin levels were similar between the groups, there were differences in TOS and OSI values. We considered these results as beneficial effect of administration albumin against IR-induced damage.

Some studies showed that follicle degeneration increased in IR groups compared to control groups in their experimental IR model investigations on ovaries.[1,4,22-25] Some researchers discovered that follicle degeneration was higher in IR groups in experimental IR ovarian model investigations.[26,27] In this study, there were significant variations in follicular degeneration between the groups. Follicle degeneration was observed to be considerably higher in the IR group than in the other groups. This shows that albumin inhibits follicle degeneration.

In some studies that used 3-hour each ischemia and reperfusion in an experimental IR model on ovaries, it was stated that the hemorrhage in IR groups increased compared to other groups.[3,28-31] We found that there was no difference between the groups in terms of hemorrhage in our study which used 2 hours each ischemia and reperfusion. However, it was found that the hemorrhage was partially higher in the IR-applied groups compared to the control group. In this case, we think that the applied ischemia and reperfusion durations are decisive in terms of hemorrhage.

Researchers discovered that vascular congestion increased in the IR-applied groups compared to the control group in their investigation, in which they constructed an ovarian IR model.[2,4,22,23,28] In this investigation, there was no difference in vascular congestion across the groups. As in hemorrhage, we believe that the applicable IR durations are critical in this scenario.

In experimental ovarian IR model investigations, some researchers found that IR groups had the most edema.[17,26,27] The other researchers, on the other hand, observed that edema was greater in the IR group than in the control group in their research in which they produced an IR ovarian model.[3,31] Decently, a substantial difference was identified between the control group and the placebo group in this investigation. The results in our albumin and IR groups were similar to those in the placebo and control groups. This discrepancy is thought to be caused by saline supplied as a placebo, which increases the amount of edema in the placebo group.

Researchers noted that the IR groups had the greatest total score in the ovarian investigations in which they constructed an IR model.[1,24] In comparable IR ovarian experiments, scientists observed that IR treatment significantly raised the total score.[22,32] In this study, there was a significant difference in total scores between the control group and the placebo and IR groups. The fact that the total score in the albumin-treated group was similar to the control group and slightly lower than the other IR-treated groups showed that albumin provided some histological protection.

A study found that CYC1 transcription increased in IR groups in their research of the cerebral IR model.[33] Other studies showed that there was no change in CYC1 immunoreactivity between the IR and control groups in their investigation done in isolated rat hearts.[34]Another study declared that when they analysed the ovaries with fluoride, the CYC1 immunoreactivity was strongerin the granulosa cells in the fluoride groups than in the control group.[35] In our investigation, CYC1 immunoreactivity was considerably higher in the IR-treated groups than that in the control group. However, because the level of CYC1 immunoreactivity in the albumingroup was much lower than in the placebo and IR groups, it is thought that albumin administration protects the tissue by lowering CYC1 immunoreactivity.

CONCLUSION

According to biochemical investigations, oxidative stress is decreased, particularly in the albumin group treated with IR when compared to the IR group. The groups had no differences in blood serum albumin or calcium levels. Histological tests revealed that the size of tissue damage increased considerably in the albu-

min, placebo, and IR groups compared to the control group. The fact is that CYC1, an indication of tissue damage, displayed greater immunoreactivity in the IR and placebo groups than in the control and albumin groups. These results indicated that albumin had a tissue damage-reducing impact. To minimize tissue damage induced by ischemia in ovarian torsion, detorsion should be administered as soon as feasible.

As a result, we believe that albumin, which has been shown to lower elevated CYC1, ROS, and oxidative stress levels, will play a supporting role in the IR therapy process due to its antioxidant properties. More detailed research is needed to back up the impact of albumin, which is a safe antioxidant.

Ethics Committee Approval: Permission for this study was given by Kafkas University Animal Experiments Local Ethics Committee (Decision Date: 23-09-2021) (Decision No: 2021-138).
Peer Review: Externally independent.
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Conflict of Interest: As the authors of this study, we declare that we have no conflict of interest.
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WHICH TOOL IS THE BEST GUIDE OPTIMIZE THE VORICONAZOLE DOSAGE: THERAPEUTIC DRUG MONITORING OR CYTOCHROME P450 POLYMORPHISM?
HANGİ ARAÇ VORİKONAZOL DOZUNU OPTİMİZE ETMEK İÇİN EN İYİ REHBERDİR: TERAPÖTİK İLAÇ İZLEME Mİ YOKSA SİTOKROM P450 POLİMORFİZMİ Mİ?

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ABSTRACT

Voriconazole (VCZ) is the drug of choice for invasive aspergillosis (IA). However, narraow the rapeuticrange and variable pharmaco kinetics can effect the success of the therapy. VCZ serum concentration is influenced by several factorin cluding CYP450 polymorphisms primarily by CY2C19. The rapeutic drug monitoring (TDM) of VCZ is highly recommended to check adequate serum concentrations. Here in, we investigated the usefulness of detecting CYP450 polymorphism. Patients with hematological malignancies were included in the study. CYP450 polymorphisms which are responsible for metabolism of VCZ were investigated using RT-PCR. TDM of VCZ was peformed using LC/MS/MS.11 patients were included in the study. Frequencies of CYP2C19 geno types are 27% for intermediate metabolizer; 36% rapid metabolizer, 18% for ultra rapid metabolizer, 18% for normal metabolizer. Two patient sexperienced dose related side effects and one of these patient's voriconazole blood concentration was supratherapeutic Although VCZ is the drug of choice for the treatment of IA, the variability of the pharmacokinetics can influence the success of therapy significantly. There fore implementing the pharmacogenetic testing and therapeutic drug monitoring to clinical practice might help clinicians to provide improved care to patients and improve treatment out comes.

Keywords: Antifungal activity, genotyping, voriconazole.

ÖZ

Vorikonazol (VCZ) invazifasperjilloziste (IA) tedavi seçeneklerinden biridir. Bununla birlikte ilacın darterapötik penceresi ve değişken farmakokinetiği tedavi başarısını etkilemektedir. VCZ kan konsantrasyonu kendisini metabolize eden CYP2C19 polimorfizmleri başta olmak üzere bazı faktörler tarafından etkilenmektedir. Terapötik ilaç izlemi (TDM) yeterli kan düzeyine ulaşılmasının kontrolünü sağlamaktadır. Bu çalışma kapsamında CYP450 polimorfizmlerinin saptanmasının faydasını araştırmayı hedefledik. Hematolojik malignitesi olan hastalar çalışmaya dahil edildi. VCZ' nin metabolizmasından sorumlu CYP450 polimorfizmleri RT-PCR ileve TDM ise LC/MS/MS ile yapıldı. 11 hasta çalışmayı tamamlayabildi. CYP2C19 genotiplerinin dağılımı orta dereceli metabolizör için %27, hızlı metabolizör için %36, ultra hızlı metabolizör için %18, normal metabolizör için %18 şeklindeydi. İki hasta dozla ilişkili istenmeyen etkiler yaşadı ve bu hastalardan birinin VCZ kan konsantrasyonu supraterapötik düzeydeydi. VCZ IA' da tedavi seçeneği arasında yer alsa da farmakokinetiğindeki belirgin değişiklik tedavisini etkilemektedir. Bu sebeple VCZ' nin TDM ve RT-PCR gibi metodlar klinikteki hekimin hastalara daha iyi bir bakım sağlamasında yardımcı olabilir, hastanın tedavisi daha iyi hale getirilebilir.

Anahtar kelimeler: Antifungal aktivite, genotipleme, vorikonazol

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INTRODUCTION

Voriconazole (VCZ) is a wide spectrum second generationtriazol eagent with potent activity against in vasive fungal infections including aspergillosis and candidiasis. It is the first choice drug of aspergillus infections.[1] These invasive infections are serious health problems for immune suppressed patients such as organ transplant patients and cancer patients.[2] VCZ has narrow therapeutic range and has interpatient variability. There fore, clinicians might fail to obtain an ideal therapeutic blood concentration which can result with treatment failure risk and dose dependent side effects including photo toxicity, hallucinations, neuropathy, periostitis, alopecia, and nail changes.[3,4] It shows non linear pharmacokinetics because of its limited elimination, and the blood concentration of VCZ is dependent on dosage. If VCZ dose is increased, the are aunder plasma concentration time curve will increase super proportionally, requiring dose adjustment to be performed carefully.[5,6] Therapeutic range of VCZ is 1.5-5.5 µg/mL. Checking drug-drug interactions, adjusting dosage according to renal function and body weight are important to achieve adequate VCZ concentrations. Another important factor is CY2C19 enzyme genotype that is responsible for VCZ metabolism and hepatic elimination.[7] Patients who are slow metabolizers might experience dose dependent toxicity such as hallucinations, visual disturbances, liver toxicity, photophobia, renal toxicity, and arrhythmia [QT prolongation) because blood concentrations of these patients are in supra therapeutic range.[8] On the other hand, patients who are fast metabolizers might not benefit VCZ at standard doses because of sub therapeutic serum concentrations.[9] According to our expectations, relation ship between genotype and VCZ serum level relation ship is given in Table1.

Although TDM of VCZ can guide for the optimum dosage, it is only available after several doses which can cause to miss a critical period. CYP450 polymorphism can be detected evenin patients who are at high risk for systemic fungal infections and can enable individualized dosage when VCZ treatment is required. Here in, we investigated the utility of each approach for optimizing VCZ treatment in patients with hematological malignancies. We aimed to see whether there are parallel results between TDM and genotyping results. This study was a replication effort and it is one of the studies to see genetic association with VCZ concentration in Turkish population.

MATERIALS AND METHODS

Patient volunteer selection

Voluntary patient only were included in the study. This study was approved by Erciyes University Clinical Trial Ethical committee, approval number 2015/101 and performed according to favorable clinical practice guide lines.

We conducteda prospective observational study in Erciyes University Hematology and Oncology Hospital. Patients participated in the study after giving written informed consent and the study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Eleven patients who were diagnosed with various hematological malignancies participated in the study (Table 2). Six of the sepatients required VCZ treatment during the course of their hospital stay. Treatment regimen was based on standard weight based dosing. Loading dose at 6 mg/kg/12 hours for the first day was followed by 4 mg/kg/12 hours as the maintenance dose. The treatment regimens were not modified according to pharmoco genetic testing and TDM results because the results of TDM and CYP450 polymorphism were available after their treatments were completed.

DNA Isolation

DNA was collected by whole blood, mouth was hand buccals wab (Table 2). Mouth was hand buccals wab sampling were used in patients who received allogeneic stem cell transplant[11] because the sepatients might have donor's DNA in their blood but not in their mouth epithelial cells. Whole blood sampling was used in non transplant patients. 2 mL blood were with drawned into K_2EDTA tubes ands amples were kept at 4°C until DNA isolation. DNAs were isolated on daily base and kept at -80°C until polymorphism screening. DNA isolation was performed using Roche High Pure Template Prepration kit (11796828001) per kit protocol.

Genotyping

CYP2C19*2 (19154G>A; rs4244285), CYP2C19*3 (17948G>A; rs4986893), CYP2C19*17 (-806C>T; rs12248560) all eles were determined by Roche light SNIP kit using polymerase chain reaction (PCR). This kit uses a hybridizing probe and melting curves were ana-

Table 1. Genotype and voriconazole serum concentration relation[10]

Genotype	Expected phenol type	Voriconazol level	Comment/Possible Solution
Primarily CYP2C19*17	Rapid metabloizer	Prophylactic use: Lower than therapeutic level (0.5 µg/mL) Treatment Lower than therapeutic level (1-2 µg/mL)	No response to treatment and systemic fungal worsening. /Dose should be increased or alternative medication should be considered
Primarily CYP2C19*2 or CYP2C19*3 Secondarily CYP2C9*2 or CYP2C9*3 or CYP3A4*1B or CYP3A5*3A	Slow metabloizer	Proflactic use: Higher than therapeutic level (0.5 µg/mL) Treatment Higher than therapeutic level (1-2 µg/mL); If higher than 4-5 µg/mL ALT and AST increases	Increased response to treatment. Controling fungal infection despiteun tolerable dose dependent side effects /Dose should be decreased or alternative medication should be considered

Table 2. Disease, DNA source and voriconazole use

PatientCode/Age	Disease	Genotyping material
P1/42	Acute myeloid leukemia	Whole blood
P2/23	Acutely mphocytic leukemia	Whole blood
P3/29	Acute myeloid leukemia	Whole blood
P4/39	Acute myeloid leukemia	Allogeneic transplant, buccal epithelial cell or mouth was hepithelial
P5/31	Hodgkin lymphoma	Whole blood
P6/57	Multiple myeloma	Whole blood
P7/57	Acute myeloid leukemia	Whole blood
P8/52	Acute myeloid leukemia	Allogeneic transplant, buccal epithelial cell, mouth was hepithelial
P9/72	Acute lymphocytic leukemia	Whole blood
P10/40	Aplastic anemia	Whole blood
P11/42	Non-hodgkin lymphoma	Very low leucocyte count (leucocyt openia) Buccal epithelial cell or mouth wash epithelial

lysed to determine single nucleotide polymorphisms (SNP). If none of these all eles were detected, patient were accepted as CYP2C19*1 genotype.

Therapeutic drug monitoring of voriconazole

Sampling for TDM was started at second day of VCZ treatment in patients who received intravenous (iv) treatment where as TDM was started at the fourth day in patients who received oral VCZ (Table 3). Samples were collected into K_2EDTA tubes and kept at 4^{o}C until plasma isolation. Plasma samples were kept at -80^{o}C and sent to an externall abnamed Toksilab Medical Diagnositc Labratory (Istanbul) under cold chain storage eusing dryice. VCZ levels were detected with LC/MS/MS. While concentrations lower than 1 µg/mL was accepted as sub therapeutic concentration, the concentrations higher than 5.5 µg/mL were accepted as supra therapeutic concentration.[12-14] Potential drug drug interactions between VCZ and co-administered drugs were checked by using lexicomp drug interactions module in updated database. All the data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statistical analysis

Eleven patients with ages ranging from 23 to 70 were included in the study. Descriptive analysis was performed using Systat Sigma Plot software ver 12.0 and data normal distribution was tested using Shpirowilk test. Statistical significance was accepted as p> 0.05. Allele frequency was calculated by dividing the numbers of the patients with regarding allele by the number of all the patients and the data was presented as percentage of n value.

RESULTS

Five out of 11 patients were male and all of them were Caucasian. The Mean age of the patients was 43.2±14.76 years. Most common underlying disease was acute leukemia and two patients received allogeneic stem cell transplantation (Table 2). VCZ treatment was administered to six patients diagnosed with invasive pulmonary aspergillosis. All genotyping results regarding CYP2C9, CYP2C19, and CYP3A4 are listed in Table 4. The Patients were hospitalized and on other medications but none of these medications caused drug interactions with VCZ through CYP2C19. In our study, 4 patients (P1,P5, P8,P9) had *1/*17 alleles and they were heterozy-

Table 3. Voriconazole TDM sampling chart

Voriconazole dosing regime and sampling time						
Loading dose (6mg/kg) and maintenance dose (4mg/kg) iv infusion (2x1)						
1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
$t_0$sampling (5mL)	*	*	*	*	*	*
Standard oral dosing 2 x 200 mg or 2 x 4 mg/kg iv						
1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
$t_0$sampling (3mL)	- No sampling	- No sampling	** C_{ss} achieved	** C_{ss}	** C_{ss}	** C_{ss}

* Blood sample could be taken 1 h before dosing for Cssmin sample (5mL), 5 min after dosing for Cssmax sample (3mL)
** Blood sample could be taken 1 h before dosing for Cssmin sample (5mL), 1 h after dosing for Cssmax sample (3mL)

Table 4. CYP2C19, CYP2C9,CYP3A4,CYP3A5 genotyping results

Patient-code	CYP2C9*3 A>C rs1799853		CYP2C19*2 G>A rs4244285		CYP2C19*3 G>A rs4986893		CYP2C19*17 C>T rs12248560		CYP3A4*1B A>G rs2740540		CYP3A5*3A A>G rs776746		Genotype	Voriconazole blood concentration (µg/mL)		
	Tm1 A	Tm2 C	Tm1 A	Tm2 G	Tm1 G	Tm2 A	Tm1 T	Tm2 C	Tm1 A	Tm2 G	Tm1 G	Tm2 A		Cssmin	Cssmax	Ctoxic
P1	50.49	-	-	57.38	56.97	-	50.49	60.10	51.81	-	55.65	-	CYP2C19*1/*17. CYP3A5*3A/3A			
P2	50.47	-	-	57.29	57.00	-	50.47	-	51.78	-	55.59	-	CYP2C19*17/ *17.CYP3A5*3A/3A			
P3	60.09	-	-	57.33	57.04	-	-	60.09	51.80	-	60.74	-	CYP3A5*3A/3A			
P4	60.12	-	51.89	57.22	56.96	-	-	60.12	51.82	-	55.60	-	CYP2C19*1/ *2.CYP3A5*3A/3A	1.14	2.12	-
P5	50.32	-	-	57.00	56.65	-	50.32	59.87	51.65	-	55.35	-	CYP2C19*1/ *17.CYP3A5*3A/3A	3.87	4.94	-
P6	50.44	-	51.67	56.94	56.67	-	50.44	60.02	51.54	-	55.25	60.56	CYP2C19*2/ *17.CYP3A5*1/3A	3.75	5.90	-
P7	50.67	-	-	57.36	57.01	-	50.67	-	51.81	-	55.64	-	CYP2C19*17/ *17.CYP3A5*3A/3A	3.29	5.44	-
P8	50.26	-	-	56.93	56.56	-	50.26	59.78	51.75	-	55.31	-	CYP2C19*1/ *17.CYP3A5*3A/3A	-	-	0.94
P9	50.68	-	-	57.39	57.12	-	50.68	60.28	51.35	-	55.63	-	CYP2C19*1/ *17.CYP3A5*3A/3A			
P10	59.49	-	51.40	56.62	56.22	-	-	59.49	51.27	-	54.94	-	CYP2C19*1/ *2.CYP3A5*3A/3A	-	-	11.76
P11	59.49	-	-	56.70	56.44	-	-	59.49	51.03	-	54.90	60.11	CYP3A5*1/3A			

Tm: melting temperature A: Adenine, G:Guanine, C:Cytosine, T: Thymine, $C_{ss:}$Steadystate concentration, C_{toxic}: sample collected when toxicity observed

goticrapid metabolizer (frequency, 36%). 2 patients (P2,P7) had homozygotic *17 allele and they were ultra rapid metabolizers (frequency, 18%), 2 patients (P4,P10) had *1/*2 alleles, one patient (P6) had *2/*14 alleles and they were intermediate metabolizers (frequency, 27%), 2 patients (P3, P11) had *1/*1 alleles and they were normal metabolizers (frequency, 18%).

All patients were normal metabolizers in terms of CYP2C9, CYP3A4, and CYP3A5.

All of TDM, the relation ship between genotyping and side effects is presented in Table 5. 6 of them needed VCZ treatment during their hospital visit. VCZ concentration of P4 and P5 were in normal ranges, and these patients did not experience VCZ related toxicity. These patients' genotype and VCZ levels were not correlated with each other. P6 and P7 blood concentrations were slightly above the therapeutic range and it seems that the genotype of these patients did not affect VCZ serum concentration.

Patient 8's genotype was rapid metabolizer and in parallel with this, VCZ blood concentration level was lower than expected. Despite that low concentration of VCZ, the patients experienced side effect at 3rd day of standard dosing treatment.

Patient 11 was geno typed as a normal metabolizer and VCZ level was above therapeutic range. Despite this high concentration, no hepatoxicity was detected. This patient experienced side effects on the 2nd day of treatment 1 hr after maintenance dose was given, and there fore blood sample was collected when the toxicity was recognized. This patient was on amphotericin B before VCZ treatment. Genotype and VCZ level was not compatible with achother. Interestingly these two patients did nothave dose related toxicities such as hepatoxicity, high bilirubin, AST, ALT level, etc. The treatment protocol of patient 8 is presented in Table 6. According to drug interaction data there is no interaction with VCZ. Despite the low blood concentration of VCZ, the patient experienced hallucination on the 3rdday of standard dosing regimen. Instantaneous blood sample VCZ level was low although the patient experienced hallucination. According to patient's treatment protocol no drug interactions were detected. Another reason for psychiatric side effects seen in patients might be acyclovir. According to the product information sheet, hallucination occurs very rarely after acyclo viruse at therapeutic doses.[15] There fore, patients might experience this side effect because of acyclovir instead of VCZ. Renal function plays an important role in terms of acyclovir toxicity and it is reported that dose should be adjusted carefully if renal function is impaired[16]. In our case, the patient's renal function was normal and acyclovir was being dosed accordingly but acyclovir concentration was not measured. Patient 11 was genotyped as normal metabolism and blood VCZ level was above the rapeutic window. Despite this high concentration, no hepatoxicity was detected. This patient experienced side effects on the 2nd day of treatment 1 hr after maintenance dose was given and blood sample was collected when the toxicity was recognized. This patient was using fluconazole against Candida infection. After resistance was observed, antifungal treatment was replaced by VCZ. It is

Table 5. CYP2C19 Genotyping results TDM and side effect relation

Patientcode	Disease	Expected Genotype of CYP2C19[10]	Voriconazole level (1-4 µg/mL)			Voriconazole dosings cheme	Side effects probably related to voriconazole
			Cssmin	Cssmax	Ctoxic		
P4	Acute myeloid leukemia Allogenic transplant	CYP2C19*1/*2 (Intermediate metabolizer)	1.14	2.12	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P5	Hodgkin's lymphoma	CYP2C19*1/*17 (Rapid metabolizer)	3.87	4.94	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P6	Multiple slyphoma/ Autologous Transplant	CYP2C19*2/*17 (Intermediate metabolizer)	3.75	5.90	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P7	Acute myeloid leukemia	CYP2C19*17/*17 (Ultra rapid metabolizer)	3.29	5.44	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P8	Acute myeloid leukemia. Allogenic transplant	CYP2C19*1/*17 (Rapid metabolizer)	-	-	0.94	2x200 mg standard dosing	Hallucination and nightmare that continue whole night
P11	Non-Hodgkin's lymphoma Autologous Transplant	CYP2C19*1/*1 (Normal metabolizer)	-	-	11.76	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	Visual disturbances. photophobia

Clinical Pharmaco genetics Implementation Consortium guide line supplement S1 for diplo types is used for determining genotype.

known that VCZ's in vitro efficacy is higher than fluconazole against Candida spp.[17] There fore, antifungal treatment choice was right in this case but supratherapeutic levels of VCZ might have caused visual side effects. According Table 6, there is not anyother medication that causes this type of effect in patient's treatment plan.

tients who experienced VZ toxicity were P8 and P11.P11's expected phenotype was normal metabolizer and despitehat serum VCZ level was at supra therapeutic level. P8 was rapid metabolizer and VCZ blood level was sub therapeutic. According to these two patient's results genotype is not always a good tool to predict

Table 6. P8 and P11 treatmen tprotocols

Initials	Patient code	Sampling type	Medications being used at that week	Dosing regime	Active ingredient	Toxicity
S.F	P8	Potential toxicity	Duphalac 670 mg	3x1	Lactulose	Hallucination andnightmare thatlastswhol enight
			Aklovir 200 mg	2x1	Acyclovir	
			Antepsin	4x1	Sucralfate	
			Leucostim 45 MIU	1x1	Filgrastim	
			Desferal 0.5g	1x1	Deferoxamine	
			Nevofam 20 mg	2x1	Famotidine	
			Methylprednisolone 250 mg	1x1	Methylprednisolone	
			Urikoliz	1x1	Allopurinol	
Initials	**Patient code**	**Sampling type**	**Medications being used at that week**	**Dosing regime**	**Active ingredient**	**Toxicity**
H.K	P11	Potential toxicity	Asirax 250 mg	2x1	Acyclovir	
			Leucostim 30 MIU	1x1	Filgrastim	
			Maxipen 1 g	3x1	Meropenem	
			Metronidazole 500 mg	4x1	Metronidazol	Photophobia, visualdisturbances
			Protaz 400 mg	1x1	Pantoprazole	
			Setrex 3 mg	2x1	Granisetron	
			Vancomax 500 mg	2x1	Vancomycin	

DISCUSSION

Personalized medicine has two key factors, which are choosing the right drug and adjusting the dosage for the patient appropriately. Drugs like VCZ which have irreversible organ toxicity, non liear kinetics and narrow therapeutic range, metabolized by CYP450 enzymes need additional approaches like therapeutic drug monitoring and pharmacogenomic analysis for correct dosead justing. These two tools might be used together to fully individualize the treatment especially for CYP450 polymrophisms. Although adjusting the dosage using only pharmacogenomic data might be considered but blood concentration should also be checked to see whether or not the drug is at therapeutic range. Besides blood sample can be drawn instantly when a suspicious reaction occurs to determine whether the drug in question is the real cause of this suspicious reaction. We conducted our study according to this logic and we collected momentary blood samples when a suspicious reaction occurred during the standard therapeutic drug monitoring process. Although genotyping is not always correlated with TDM, we observed itin our study. Padrug concentration because it should be remembered that when a genotyping analysis is performed, it only gives an idea about the patient's expected phenoyte, not real life results. In addition analyzing the phenotype is harder than TDM and genotyping because samples should be taken when patient is not receiving any treatment, and phenotype is affected by environmental factors so much. In addition, P4,P5,P6,P7 did not experience any VCZ toxicity and their VCZ concentrations were in therapeutic ranges. It seems that genotype did not affect VCZ concentration.

The limitation of our study was the number of the patients. It was because systemic fungal infections and concomitant chronic diseases might be a cause of death in hematological malignancy patients and during the study we genotyped nearly 50 patients but most of them were deceased and thus the frequency of the patients who suffered from fungal infections were low. For these reasons the number of the patients was limited in our study.

In general, clinicians observe toxicities in the patients who have hematological malignancies. Medications in

the treatment plan should be monitored carefully in terms of toxicities, blood concentration and inter individual variances. In patients who have malignancies and use multiple drugs side effect monitoring sholud be performed regularly. TDM is such a nice tool that it can be used to show whether the reactions in patients are actually caused by the drug concerned or other factors. The rapeutic drug monitoring might help monitor patients because in one of our cases hallucination was probably caused by acyclovir instead of VCZ, because the VCZ was at sub therapeutic concentration[18]. In another case therapeutic drug monitoring revealed that VCZ is the cause of hallucination. In addition, at supra therapeutic VCZ level, these patients are potentially at risk for other dose dependent side effects such as hepatoxicity. Although health authorities do not force to test for CYP2C19 polymorphisms for VCZ, pharmacogenomics might be a good tool to check potential side effects that might be experienced. It is clear that the patients with homozygotic CYP2C19 slow metabolizer will highly experience dose dependent side effects of VCZ and other medications which are inactivated by this CYP2C19. If patient's pharmacogenomic data is available at clinician's hand, this data should be used when other CYP2C19 substrates are prescribed as well. Consequently, one time genotyping is good for adjusting or having a clue for potential dose related side effects of all medications. Additionally, therapeutic drug monitorin gshould be added to support polymorphisms which change pharmacokinetics of a drug.

CONCLUSION

Therapeutic drug monitoring might help in monitoring patients because in one of our case hallucination is probably caused by acyclovir instead of VCZ, because the VCZ was at sub therapeutic concentration. In general pharmacogenomic analyses are performed to predict the treatment out come but therapeutic drug monitoring should support genomic data and it is another important tool to monitor patient's response.

The survival expectancy of the patient population included in the study was low, only 11 patients completed the study. Nearly 40 patients were screened but most of them were deceased during the study because of disease progression. No statistical report was generated because of this.

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Informed Consent: Patients participated in the study after giving written informed consent and the study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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ANALYSIS OF VOLATILE COMPOUNDS OF *ALCEA CALVERTİİ* BOİSS. AND ITS ANTIMICROBIAL, ANTICHOLINESTERASE AND ANTITYROSINASE POTENCY

ALCEA CALVERTİİ BOİSS.'İN UÇUCU BİLEŞENLERİNİN ANALİZİ AND ANTİMİKROBİYAL, ANTİKOLİNESTERAZ VE ANTİTİROZİNAZ ETKİSİ

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ABSTRACT

The research aimed to analyze the volatile compounds by using SPME-GC-MS and to detect anticholinesterase, antityrosinase, and antimicrobial potential of metanol extract of *Alcea calvertii* Boiss., an endemic species for Türkiye. The inhibitory effects of tyrosinase, acetyl cholinesterase, and butyrylcholinesterase of the plant were determined by spectroscopic technique and the plant's antimicrobial activity was assessed using the agar diffusion method. A total of 18 volatile compounds were specified belonging to terpenes classes. *o*-cymene (10.60%) and sesquicineole (15.55%) were detected as major volatile components of the species by the SPME-GC-MS technique. Meaningful antimicrobial activity was observed on *Candida tropicalis, Enterococcus faecalis, Escherichia coli, Mycobacterium smegmatis, Staphylococcus aureus,* and *Pseudomonas aeruginosa*. The half maximal inhibitory concentration (IC_{50}) value of the plant was determined 60.12 ± 1.75 µg/mL as a result of tyrosinase assay. IC_{50} value was found 111.54 ± 1.75 µg/mL, according to butyrylcholinesterase inhibition studies. Considering all the findings, it has been determined that the plant includes diverse volatile compounds and showed promising antimicrobial, tyrosinase inhibitory, and moderate butyrylcholinesterase inhibitory effects so *Alcea calvertii* may be the up-and-coming source of natural medicine for microbial and dermatological diseases although limited to its effects for Alzheimer's disease.

Keywords: *Alcea calvertii* Boiss., ant cholinesterase, antimicrobial, antityrosinase, GC-MS.

ÖZ

Bu araştırmanın amacı Türkiye için endemic bir tür olan *Alcea-calvertii* Boiss'in uçucu bileşenlerin SPME-GC-MS kullanılarak analiz edilmesi ve bitkinin methanol ekstresinin antikolinesteraz, antitirozinaz ve antimikrobiyal potansiyelinin belirlenmesidir. Türün tirozinaz, asetilkolinesteraz ve bütirilkolinesterazin hibitör etkileri spektroskopik teknikle belirlenmiş olup, antimikrobiyal aktivitesi için agar difüzyon yöntemi kullanılmıştır. Çalışma sonucunda terpenler sınıfı ait toplam 18 uçucu bileşen belirlenmiştir. SPME-GC-MS tekniği ile belirlenen uçucu bileşenelerinden *o*-simen (%10.60) ve seskisinol (% 15.55) türün ana uçucu bileşenleri olarak tespit edilmiştir. *Candida tropikalis, Escherichia coli, Enterococcus faecalis, Mycobacterium smegmatis, Pseudomonas aeruginosa* ve *Staphylococcus aureus* üzerinde ekstrenin anlamlı antimikrobiyal aktivite gösterdiği gözlemlenmiştir. Antitirozinaz aktivite çalışmaları sonucunda ekstrenin yarı maksimum inhibisyon konsantrasyonu (IC_{50}) değeri 60.12 ± 1.75 µg/mL olarak belirlenmiştir. Bütirilkolinesteraz inhibisyon çalışmalarına göre IC_{50} değeri 111.54 ± 1.75 µg/mL olarak tespit edilmiştir. Tüm bulgular gözönüne alındığında, türün zengin uçucu bileşen içeriğine sahip olduğu ve ümit verici antimikrobiyal, tirozinazinhibitör ve orta derecede bütirilkolinesteraz inhibitor etkiler gösterdiği, dolayısıyla *Alcea calvertii*'nin Alzheimer hastalığı için tedavi edici değeri sınırlı olmakla birlikte mikrobiyal, dermatolojik ve gelecek vaat eden doğal ilaç kaynağı olabileceği değerlendirilmiştir.

Anahtar kelimeler: *Alcea calvertii* Boiss., antikolinesteraz, antimikrobiyal, antitirozinaz, GC-MS.

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INTRODUCTION

Plants possess comprehensive utilizations for different purposes for a long time.[1] Medicinal and aromatic plants have been utilized in the protection of health, prevention, and treatment of diseases for many years. Also, they are utilized in the field of food as dietary supplements, herbal tea, or flavor. In addition, they are used in perfumery and cosmetic industries as body care products.[2-4] So, phytochemical and biological activity studies on natural sources present new opportunities for scientific and industrial areas.

Alcea L. genus (Malvaceae) is represented by about 70 species in the world. The genus is found in Asia, especially in Iran and Türkiye. *Alcea calvertii* Boiss., one of the endemic species for Türkiye, is growing in Tunceli province. *Alcea* species have been used for anti-inflammatory effects, cough, intestinal disorders, kidney stones, pulmonary disorders, skin disorders, stomach ailments, urinary system disorders, etc., as a folk medicine for a long time. According to previous biological activity studies, *Alcea* species have diverse medicinal activities such as antioxidant, antimicrobial, antiviral, and hepatoprotective effects. *A. calvertii* has been used for kidney stones, lung disorders, pulmonary disorders, skin disorders, stomach disorders, and urinary system disorders, traditionally, too.[2,5,6]

The cholinergic system plays a vital role in brain functions. Acetylcholine (ACh) is accepted as a significant neurotransmitter for synaptic transmission of cholinergic system. Acetyl cholinesterase (AChE) and butyrylcholinesterase (BuChE) are enzymes in charge of hydrolysis of acetylcholine in synapse. Cholinesterase inhibitors inhibit the degradation of acetylcholine, thereby enhancing central and peripheral cholinergic function. ACh is hydrolysed by the AChE to allow the further transmission of impulses after the mediation of the impulse transmission. Another type of ChE, known as BuChE, is distributed all over the body and has a range of physiological roles. BuChE is discovered to play a role in both normal cholinergic function, and also the formation and progression of Alzheimer's Disease. AChE is the primary enzyme in the normal brain, while BuChE acts as a supporter when ACh concentrations are high. It has been suggested that in order to preserve optimal brain function, BuChE may assist the hydrolysis of excess ACh in the cholinergic system and balance to substrate-inhibited AChE. Cholinesterase inhibitors cause the rise of low choline levels and are clinically used in Alzheimer's Disease.[7]

Tyrosinase (TYR) enzyme is important in hyperpigmentation problems such as skin spots caused by excessive melanin synthesis in the body. Therefore, agents that inhibit TYR enzymes can be used to treat hyperpigmentation problems.[8-10]

Essential oils are oily mixtures obtained by water or steam distillation, which can be found in liquid or frozen form at room temperature. Essential oils obtained from plants are an indispensable part of the pharmaceutical, food, and cosmetic industries. The vast majority of essential oils (about 90%) are composed of terpenic substances. In chemical terms, terpenes are defined as a group of molecules that have a diverse but specific number of isoprene units. In recent years, natural antimicrobial agents have compelled the attention of both food and medicine industries due to their potential applications as food and medicine preservatives. Some secondary metabolites and essential oils found in plants can be used as food and medicine preservatives because of their antimicrobial effects for this purpose.[11,12]

Plant essential oils have been used frequently in cosmetic, food, and medicine areas for many years. So, the attention on obtaining, detecting, and quantifying natural volatile compounds has been scaling up for the food and medicine industries daily. Solid phase microextraction (SPME) is one of the detection and quantification techniques of natural volatile organic compounds which possess lots of advantages like running without solvent, portability, the probability of automation, rising sensitivity, passive sampling, etc.[13,14]

In light of all this information, the targets of this study were to carry out SPME-GC-MS analysison the species and to evaluate the antimicrobial and enzyme inhibition properties of *A. calvertii.*

MATERIAL AND METHODS

Chemicals and Instrumentation

Mushroom tyrosinase (EC 1.14.1.8.1, 30 U), levodopa (L -DOPA), disodium phosphate, sodium dihydrogen phosphate, 5,5′-Dithiobis(2-nitrobenzoic acid) (DTNB), acetylcholinesterase from *Electrophorus electricus* (electric eel) (AChE), acetylthiocholine iodide, butyrylcholinesterase human (BChE), butyrylcholine iodide, and galanthaminehydrobromide from *Lycoris* sp., were provided from Sigma-Aldrich. Methanol was purchased from Merck (Darmstadt, Germany). All microorganisms used in antimicrobial studies were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Türkiye). Ampicillin and fluconazole were purchased from Mustafa Nevzat and Pfizer, respectively. Mueller Hinton agar and broth, potato dextrose agar, brain heart ı-infusion agar (BHI), and broth were purchased from Merck (USA). All absorbance values were determined using a BMG LABTECH SPECTROstar® Nano spectrophotometer. Evaporation procedures were employed using the Heidolph rotary evaporator system (Schwabach, Germany). A manual fıber SPME device was obtained from Supelco (USA). GC analysis was carried out using a Shimadzu 2010 Plus (USA) device attached to a Shimadzu QP2010 (USA) Ultra mass selective detector and flame ionization detector concurrently.

Plant Material and Preparation of Samples

A. calvertii specimens were collected in 2017 from Erzincan, Türkiye and were identified by Prof. Dr. Ali KANDEMİR. The species was deposited in the Erzincan Binali Yildirim University Science Faculty herbarium (Herbarium Number: 10955). Primarily, the aerial parts of the plant were dried in the shade at room temperature and properly powdered. Forty grams of dried plant material was extracted with 400 mL methanol overnight at room temperature three times. The methanolic extract was filtered, and afterward, the filtrate was evaporated using a rotary evaporator to dry. The obtained extract was stored at 4 °C for use in biological studies.

SPME-GC-MS Analysis

Solid-phase microextraction

Polydimethylsiloxane/divinyl-benzene (PDMS/DVB, 65

µm-blue hub plain) fiber was identified in a manual fiber SPME device incorporated for exposing volatile components; the fiber was preconditioned for 30 minutes at 250 °C in the GC injection port. Following the sample process, the SPME device was inserted into the GC and GC-MS injectors for the duration of the 62-minute GC analysis on an RTX-5M column. The SPME fibers were prepared in the GC injector at 250 °C for 30 minutes. At 50 °C, extractions were achieved after 30 minutes of incubation and 10 minutes of extraction.

Gas chromatography-mass spectrometry/flame ıonization detector (SPME-GC-MS-FID)

Approximately 1.00 g of plant material was added to a 10-mL vial as part of the SPME method. Each extraction process used magnetic stirring. Next, in split mode, fibers containing extracted aroma components were introduced into the GC injector with a split ratio of 1:10. For four minutes, thermal desorption was conducted at 250 °C. To help with the separation processes, a Restek Rxi-5MS capillary column was used. After two minutes at 60 °C, the oven's temperature was raised to 240 °C at a rate of 3 °C per minute, and it was then maintained at 250 °C for an additional four minutes. The carrier gas used in this experiment was helium (99.999%), flowing at a steady flow rate of 1 mL/min. After the ionization voltage was stabilized at 70 eV, the electronic impact mode was employed for detection. A mass acquisition in scan mode (40-450 m/z) was carried out. For identification, each volatile molecule was compared to its corresponding RI (concerning the C7–C30 alkane standards). Mass spectrum data were compared with those stored in the Wiley and NIST library of mass spectra, as well as the FFNSC1.2 and previous literatures[15]

Antimicrobial Activity

In this work, *Escherichia coli* ATCC 25922, *Yersinia pseudotuberculosis* ATCC 911, *Klepsiella pneumonias*ubp. *pneumonia* ATCC 18883, *Pseudomonas auroginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Bacillus cereus* 702 Roma, *Mycobacterium smegmatis* ATCC607, *Candida albicans* ATCC 60193 *Candida tropicalis* ATCC 13803, and *Saccharomyces cerevisiae* RSKK 251 were selected as test microorganisms. Ampicillin (10 µg) for antibacterial activity and fluconazol (5 µg) for antifungal activity were used as standard drugs. Mueller Hinton agar and broth for gram (-) and gram (+) bacteria, potato dextrose agar for yeast-like fungi, BHI, and broth for *M. smegmatis* were used. In this study, antimicrobial activity was determined by applying some changes in the agar disc diffusion method.[16]

Tyrosinase (TYR) Inhibitory Effect

The TYR inhibitory effect of the plant was determined with the Masuda method.[17] Different concentrations of methanolic extract (25, 50, 100, and 500 µg/mL), TYR solution (46 U/mL), and phosphate buffer (0.2 M, pH 7.0) were prepared and transferred to the microplate. This mixture was incubated for 10 min at 23°C. Later, L-DOPA solution (2.5 mM) was added to all wells. After incubating for 10 min at 23°C, the absorbance of this mixture was read at 490 nm using a spectrophotometer. Kojic acid used as standard was prepared in various concentrations (25, 50, 100, and 500 µg/mL), and the TYR inhibition effect was determined with the same assay.

Cholinesterase Inhibitory Effect

The anticholinesterase activity of the methanol extract was examined using Ellman's assay with some modifications.[18] The methanolic extract (25, 50, 100, and 200 µg/mL), AChE (0.2 U/mL) BuChE (0.2 U/mL), and phosphate buffer (10 mM, pH 8) were respectively put in an Elisa plate and incubated for 15 min at 25°C. Then, DTNB (10 mM) and acetylthiocholine iodide (15 mM) or butyrylthiocholine iodide (15 mM) (substrate) were added to all wells and incubated for 10 min. The absorbance was measured spectrophotometrically at 412 nm. Galantamine in various concentrations (25, 50, 100, and 200 µg/mL) was used as standard in this experiment.

Data Analysis

All experiments were conducted at least three times. Statistical significance differences between the data were expressed as means ± standard deviations (SDs). GraphPad Prism 8.0.1 (244) was used for the calculation and to create graphs.

RESULTS

Chromatographic separation is based on the principle that first low molecular weight compounds are entrained in the column and then high molecular weight compounds are entrained. Qualitative analysis of the separated volatile compounds was made by comparing the index values obtained from the mass spectra with the library retention index values. Volatile components of the plant were determined for the first time in this study. Volatile components of the extract of *A. calvertii* were investigated by SPME-GC-MS analysis and results were presented in Table 1-3. Extract of *A. calvertii* was comprised of monoterpenes (12.00%), monoterpenes derivatives (12.92%), sesquiterpenes (37.71%), sesquiterpenes derivatives (10.02%), and sesquiterpenoid (5.85%) (Table 1). The most abundant volatile components found in the plant are o-cymene (10.60%) and sesquicineole (15.55%) (Table 2).

Additionally, a total of 18 volatile compounds identified as 2-hexenal, benzaldehyde (CAS), α- phellandrene, n-octylacetylene, o-cymene, *β*-phellandrene, α-

Table 1. The chemical class distribution of the essential oil components of *A. calvertii*

Compound Class	%Area	Number of compounds
Monoterpenes	12	2
Monoterpenes Derivatives	12.92	3
Sesquiterpenes	37.71	7
Sesquiterpenes Derivatives	10.02	3
Sesquiterpenoids	5.85	1
Others	12	3

Table 2. The major components in the chemical class distribution of the essential oil constituents of *A. calvertii.*

Compound class	Major component	% Area	RI
Monoterpenes	o-cymene	10.60	1026
Monoterpenes Derivatives	α- phellandrene	8.37	1007
Sesquiterpenes	Sesquicineole	15.55	1516
Sesquiterpenes Derivatives	Trans-*β*-caryophyllene	4.52	1426
Sesquiterpenoids	Copaene	8.65	1380
Others	Benzaldehyde	5.44	966

terpinene, copaene, 7-epi-sesquithujene, trans-*β*-caryophyllene, α-bergamotene, (E)-*β*-farnesene, *β*-cubebene, α-curcumene, *β*-bisabolene, sesquicineole, carotol and *β*-bisabolol were determined with SPME-GC -MS method (Table 3, Figure 1-2).

The antimicrobial activity of *A. calvertii* was specified using the agar disc diffusion method and the results were listed in Table 4. *A. calvertii* was found effective against bacteria of *E. coli*, *P. aeruginosa*, *S. aureus*, *E. faecalis* and *M. smegmatis*.

TYR inhibitory effect of methanolic extract of *A. calvertii* was investigated modified dopachrome method. Percentage (%) inhibitions of TYR of the kojic acid were found 31.25 ± 0.71, 43.13 ± 1.17, 67.5 ± 0.82, 98.13 ± 1.31 µg/mL for the 25, 50, 100, and 500 µg/mL, respectively (Table 5). Percentage (%) inhibitions of TYR of the methanolic extract of A. calvertii were found 26.88 ± 1.23, 51.75 ± 0.57, 65.63 ± 1.05, 83.75 ± 1.24 µg/mL for the 25, 50, 100, and 200 µg/mL. The methanolic extracts of the plant half-maximal inhibitory concentration (IC_{50})

Table 3. Major volatile components of *A. calvertii*based on SPME-GC/FID-MS analysis.

Retention Time	Compound Name	% Area[a]	Retention Index[b]	Compound Classification
10.27	2-Hexenal	3.40	861	alkyl aldehyde
14.29	Benzaldehyde (CAS)	5.44	966	aromatic aldehyde
15.98	α- phellandrene	8.37	1007	cyclic monoterpene
16.55	n-Octylacetylene	3.16	1020	alkyne
16.81	o-cymene	10.60	1026	monoterpene
17.05	*β*-phellandrene	4.55	1032	cyclic monoterpene
19.54	α-Terpinene	1.40	1090	monoterpene
31.70	Copaene	8.65	1380	sesquiterpenoid
32.12	7-Epi-sesquithujene	1.80	1390	sesquiterpene
33.54	Trans-*β*-caryophyllene	4.52	1426	bicyclic sesquiterpene
33.94	α-Bergamotene	3.33	1437	sesquiterpene
34.57	(E)-*β*-farnesene	5.85	1453	sesquiterpenoid
35.50	*β*-cubebene	2.93	1478	tricyclic sesquiterpene
35.69	α-Curcumene	1.28	1483	sesquiterpene
36.67	*β*-bisabolene	5.22	1508	sesquiterpene
36.93	sesquicineole	15.55	1516	sesquiterpene
40.18	Carotol	1.87	1605	sesquiterpene
42.58	*β*-bisabolol	2.57	1674	monocyclic sesquiterpene
Total		90.50		

a,: % Area obtained by FID peak-area normalization; b,: RI calculated from MS, retention times relative to that of n-alkanes (C6-C30) on the nonpolar Restek Rxi-5MS column.

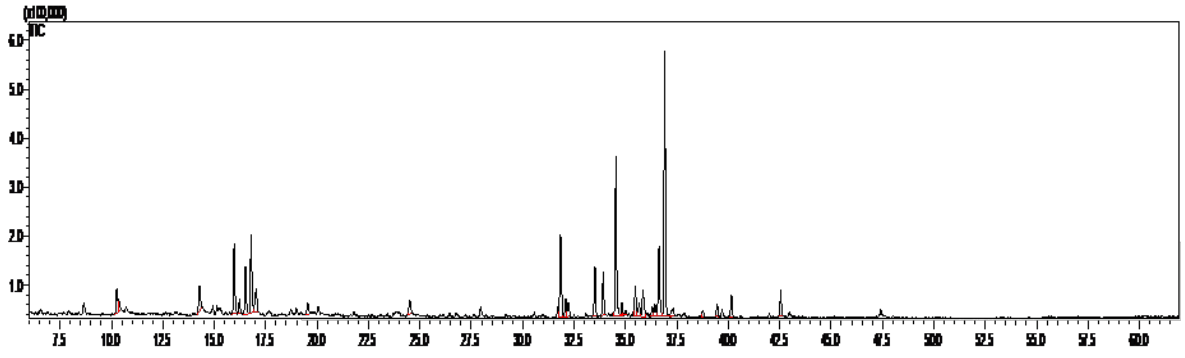

Figure 1: MS Spectrum of *A. calvertii*

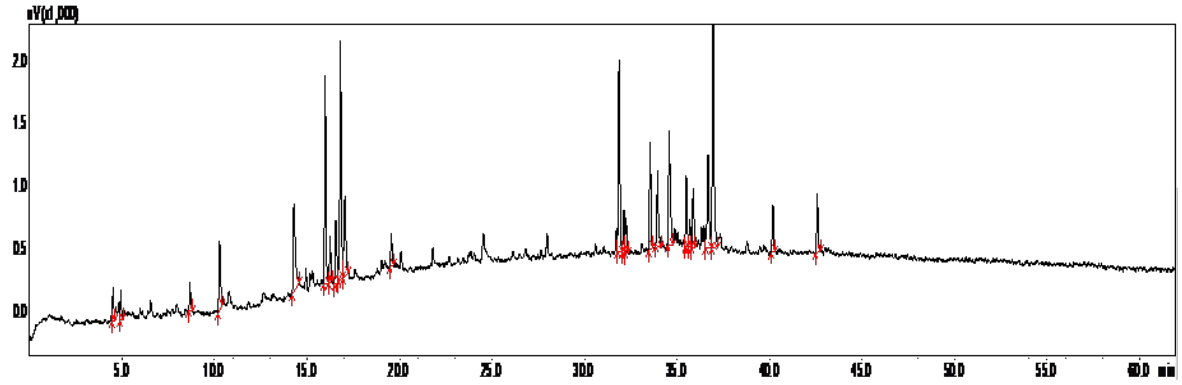

Figure 2: FID Spectrum of *A. calvertii*

Table 4. Antimicrobial activities of methanolic extract of *A. calvertii*(mm).

Tested Compounds	Microorganisms and Inhibition Zone (mm)										
	Gram-negative				Gram-positive			No gram	Yeast Like Fungi		
	Ec	Yp	Kp	Pa	Sa	Ef	Bc	Ms	Ca	Ct	Sc
The methanolic extract of *A. calvertii*	10	6	6	10	10	12	6	10	6	12	6
Ampicillin	10	10	10	18	35	10	15				
Streptomycin								35			
Fluconazole									25	25	25

Ec,:*E. coli* ATCC 25922, **Yp,:** *Y. pseudotuberculosis* ATCC 911,**Kp,:** *K. pneumonia*subp. *pneumonia* ATCC 18883, **Pa,:** *P. aeruginosa* ATCC 27853, **Sa,:** *S. aureus* ATCC 25923, **Ef,:** *E. faecalis* ATCC 29212, **Bc,:** *B. cereus* 702 Roma, **Ms,:** *M. smegmatis* ATCC607, **Ca,:** *C. albicans* ATCC 60193, **Ct,:** *C. tropicalis* ATCC 13803, **Sc,:** *S. cerevisiae* RSKK 251

value (60.12 ± 1.75 µg/mL) was similar to kojic acid (57.41 ± 1.03 µg/mL).

Cholinesterase inhibitory activity of the methanolic extract was examined in this study. The AChE percentage inhibition of the methanolic extract and galantamine is given in Figure 3. IC_{50} values of the methanolic extract of *A. calvertii* and galantamine were found 576.88 ± 2.35 and 8.07 ± 1.15 µg/mL, respectively. According to the BuChE inhibition test, IC_{50} values of the galantamine and the methanolic extract of *A. calvertii* were detected as 29.25 ± 2.35 µg/mL and 111.54 ± 1.71 µg/mL, respectively.

DISCUSSION

Most plants possess peculiar smell and aromatherapeutic properties because of their qualified volatile contents.[9,19] Many researchers have focused on plants' volatile contents which have many functional features such as antimicrobial, antiviral, antioxidant, and anticancer.[20,21] In this present study, volatile components of *A. calvertii* plant were identified by SPME-GC-MS. As stated in Table 1, the classification of the volatile components from *A. calvertii* was consisted of monoterpenes, sesquiterpene, and sesquiterpenoid. The major volatile components of *A. calvertii* were determined as *o*-cymene and sesquicineole. Terpenes provide lots of protective functions for the organism. In addition, terpenes possess significant biological activities such as antimicrobial, antifungal, and antimalarial properties.[11,22,23] Furthermore, volatile terpenoids has been proven to be as potential drug leads in Alzheimer's disease by ChE inhibition[24]. So *A. calvertii*, which includes

Table 5.TYR inhibitory effects of (% inhibition) of methanolic extract of *A. calvertii*

Samples	25 µg/mL	50 µg/mL	100 µg/mL	500 µg/mL	IC_{50} (µg/mL)
The methanolic extract of *A. calvertii*	26.88 ± 1.23	51.75 ± 0.57	65.63 ± 1.05	83.75 ± 1.24	60.12 ± 1.75
Kojic acid	31.25 ± 0.71	43.13 ± 1.17	67.5 ± 0.82	98.13 ± 1.31	57.41 ± 1.03

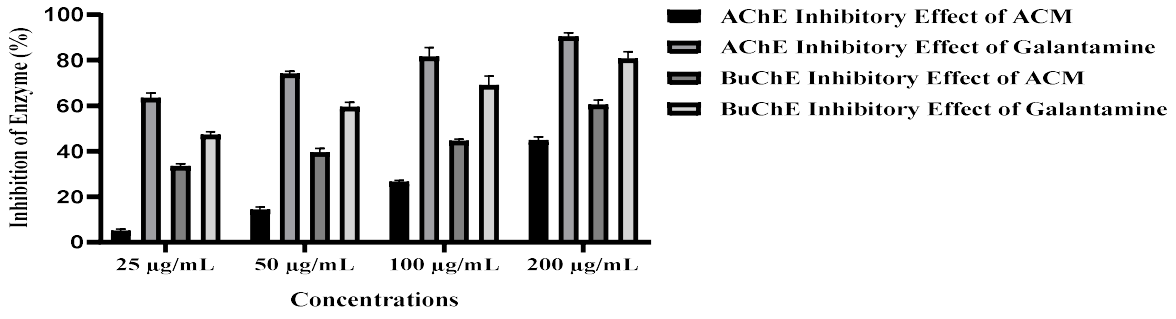

Figure 3: AChE and BuChE inhibitory effect (% inhibition) of methanolic extract of *A. calvertii* (ACM)

volatile components that belong to terpenes classes, can be a natural source of medicine for human health. It is the first study about SPME-GC-MS analysis of *A. calvertii*, but there are several studies about other *Alcea* species. A total of 28 terpenes were determined by GC-MS in the study on *Alcea nudiflora*.[25] Also, 24 terpenes and 29 terpenes were detected by GC-MS analysis for *Alcea pallida* and *Alcea apterocarpa*, respectively.[26]When the previous studies are compared with the present study, common volatile components were not detected between the *Alcea* species. The volatile compound differences of *Alcea* species can be related to typical properties or climatic, seasonal, and geographical factors. Other GC-MS analyses of *Alcea* species such as *Alcea rosea*, *Alcea pallida* are generally about fixed oil of the species.[2,27]

Nowadays, the importance of antimicrobial research has increased due to the rapid spread of antibiotic-resistant bacteria and microorganisms. Besides, the success rate against multiple antibiotic resistance in treating infection is decreasing gradually. Medicinal plants as an alternative to synthetic drugs continue to be important for antimicrobial treatments.[28,29] For this purpose, the antimicrobial activity of *A. calvertii* was determined in the current study. According to the data given in Table 4, the methanolic extract of aerial parts of *A. calvertii* showed significant antimicrobial activities against some microorganisms. The growth inhibition zones ranged from 6 to 12 mm against microorganisms. The methanolic extract of aerials of *A. calvertii* exhibited antimicrobial activity against bacteria of *E. coli*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, and *M. smegmatis*. Compared with the effect of ampicillin, the plant showed moderate antimicrobial activity against *E. faecalis*. Activity on yeast fungus of the methanolic extract was observed against *C. tropicalis*. It has been reported that most of the subspecies of *Alcea* showed antimicrobial and antiviral activity in various studies.[5] In the previous study, *Alcea pallida* and *Alcea apterocarpa* inhibit the growth of *C. albicans*, *E. coli*, *Streptococcus pyogenes*, *S. aureus,* and *P. aeruginosa*.[26] The methanolic extract of flowers of *A. calvertii* was found to be effective on *Listeria monocytogenes*, *E. coli*, *B. subtilis,* and *C. albicans*.[17] Different effects on some microbial organisms of the same species are probably related to the selections of different parts of the plants. Also, climatic, seasonal, or geographical factors can be efficacious for this situation. Similarly, discrepancies between different *Alcea* species can be due to climate, seasonal, or geographical factors. It can also be said that the significant antimicrobial activity of *A. calvertii* is due to its volatile components.

Terpenes with antimicrobial qualities, or those that enable them to eradicate or inhibit the growth of microorganisms, are commonly used in both traditional and modern medications.[30] Studies on the antibacterial activity of β-caryophyllene have been actively conducted on its effects. According to the presented study, β-caryophyllene is the most abundant component belonging to sesquiterpenes derivatives in *A. calvertii*. Research about the antimicrobial activity of β-caryophyllene has been proven to affect both Gram-positive and Gram-negative aerobic bacteria, including *E. coli* and *S. aureus*.[31] Copaene is the most common essential component belonging to sesquiterpenes in *A. calvertii* have been proven to possess antimicrobial activity against Gram-positive and Gram-negative human pathogens.[32] Therefore, in particular, to β-caryophyllene and Copaene, all terpene components may contribute to the antimicrobial activity of *A. calvertii*.

The main task of melanin is to protect the skin from the harmful effects of ultraviolet light. TYR enzyme plays a key role in melanin synthesis. Many studies have been reported to be effective on the TYR enzyme of plant extracts.[33-36] In this study, the IC_{50} value of the *A. calvertii* extract and kojic acid were found 60.12 ± 1.75 and 57.41 ± 1.03 µg/mL. These findings have indicated that *A. calvertii* exhibited potent TYR inhibition. In the previous study about enzyme inhibition of *A. rosea*, the IC_{50} value of *A. rosea* extract was calculated as 0.38 mg/mL. *A. calvertii* is more effective than *A. rosea* for TYR enzyme inhibition compared with IC_{50} values.[16]

As mentioned before, *A. calvertii* was shown to possess high concentrations (≥4%) of *β*-caryophyllene, benzaldehyde, o-cymene, *β*-bisabolene, and sesquicineole components based on the presented study. *β*-Caryophyllene has proven to inhibit melanogenesis by downregulating tyrosinase, TRP-1, TRP-2, and MITF expression, which would lower the amount of melanin in the skin.[37] Benzaldehyde and its derivates have been evidenced to have the potential for tyrosinase inhibition.[38] Numerous herbal extracts one of the main constituents of their essential oils was determined as o-cymene have been shown to have tyrosinase inhibitory properties.[39,40] The tyrosinase inhibitory effect potential of a some plants-derived extracts which include *β*-bisabolene as marker components in their essential oil was revealed.[41] It has been demonstrated that a herbal essential oil source with high concentrations of sesquicineole and β-Caryophyllene constituents also has a strong inhibitory impact on tyrosinase at a concentration of 200 µg/mL (IC_{50}=63.30 ± 2.35 µg/mL).[42] Therefore, it may follow that these components contributed to *A. calverti*'s tyrosinase inhibitory property.

Interest in cholinesterase inhibition activity due to its importance for the treatment of Alzheimer's disease is increasing day by day. Synthetic drugs are being developed, but significant research is being continued to discover natural products that can be used for this purpose. Some studies show that some plants have traditionally been used to improve and alleviate other cognitive functions and symptoms associated with Alzheimer's disease.[12] BuChE inhibitor activity (% Inhibition) of the *A. calvertii* was found 33.25 ± 1.23, 39.26 ± 2.05, 44.35 ± 1.03 and 60.39 ± 2.16 µg/mL for the 25, 50, 100 and 200 µg/mL, respectively. AchE inhibitor activity (% inhibition) of the *A. calvertii* extract was found 4.86 ± 0.97, 14.21 ± 1.22, 26.43 ± 0.81 and 44.73 ± 1.61 µg/mL for the 25, 50, 100 and 200 µg/mL, respectively. According to the previous study, AchE inhibitory effect (% Inhibition) of the *A. pallida* and *A. apterocarpa* methanolic extracts were found 53.26 ± 1.24 and 57.07 ± 0.37 for 200 µg/mL, respectively.[26] The methanolic extracts of *A. pallida* and *A. apterocarpa* are similar but more effective than the methanolic extract of *A. calvertii* in terms of AChE inhibition. Consequently, the presented results revealed that *A. calverti* showed limited AChE and BuChE inhibitory effects like other *Alcea* species.

CONCLUSION

This study is a preliminary study to uncover the therapeutic potential of *A. calvertii* which includes abundant volatile content. It is also an original study in terms of the first SPME-GC-MS analysis, antityrosinase, and anticholinesterase activity screening studies on the plant. The plant has the potency to be used for hyperpigmentation treatments because of its inhibitory effect on the TYR enzyme. The study ensured to creation of preliminary data for using of *A. calvertii* in the treatment of various global diseases because of its cholinesterase inhibitory and antimicrobial effects. However, further studies about the determination of the compounds that are responsible for the activities, and detection of the underlying mechanism of the activities are needed to be clarified to benefit the therapeutic effects of *A. calvertii*.

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Informed Consent: The relevant research does not require approval.

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LEVELS OF AND REASONS FOR MISSED NURSING CARE FROM THE PATIENT AND NURSE PERSPECTIVE
HASTA VE HEMŞİRE PERSPEKTİFİNDEN KARŞILANAMAYAN/VERİLEMEYEN HEMŞİRELİK BAKIMI DÜZEYLERİ VE NEDENLERİ

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ABSTRACT

In terms of missing nursing care, linked with measuring how often and to what extent elements of nursing care are overlooked, identifying missed care interventions based on nurse and patient responses will pave the way for objectively assessing and developing solutions to the reasons behind missed care needs. The present study aimed to determine the levels of and the reasons for missed nursing care needs in a state hospital in Türkiye based on nurse and patient responses. This study was conducted with 172 nurses employed in the clinical divisions and 180 patients hospitalized in the clinical units. All analyses were performed on the SPSS 21.0 program. Based on the participating nurses' responses, the findings revealed the three most missed elements of nursing care assisting the patient in ambulating three times per day or as ordered, feeding the patient when the food is still warm, and turning the patient every two hours. When it comes to missed nursing care from the patient's perspective, the findings revealed the most overlooked elements of nursing care to be related to basic care: oral care, bathing, and ambulation. Overall, perceptions of nursing staff and patients were found to be similar for certain aspects of nursing care.

Keywords: Missed nursing care, nursing care, nursing care management, patient care, patient safety.

ÖZ

Hemşirelik bakımının öğelerinin ne sıklıkta ve ne ölçüde gözden kaçtığının ölçülmesiyle bağlantılı olan karşılanamayan hemşirelik bakımı açısından, karşılanamayan bakım müdahalelerinin hemşire ve hasta cevapları perspektifinde belirlenmesi; objektif bir değerlendirmenin ve bakım ihtiyaçlarını karşılanamamasının ardındaki nedenlere çözümler geliştirmenin yolunu açacaktır. Bu çalışmanın amacı, Türkiye'de bir kamu hastanesinde karşılanamayan hemşirelik bakım gereksinimi düzeyini ve nedenlerini hemşire ve hasta yanıtlarına dayalı olarak belirlemektir. Bu çalışma klinik birimlerde çalışan 172 hemşire ve klinik birimlerde yatan 180 hasta ile yürütülmüştür. Tüm analizler SPSS 21.0 programında gerçekleştirilmiştir. Katılımcı hemşirelerin yanıtları, karşılanamayan ilk üç hemşirelik bakımının sırasıyla; hastayı günde üç kez veya gerektiği kadar ayağa kaldırma/ dolaştırma, hastanın yemek henüz sıcakken beslenmesi ve her iki saatte bir hastanın çevrilmesi olduğunu ortaya koymuştur. Hasta perspektifinde karşılanamayan hemşirelik bakımı bulguları incelendiğinde ise, en sık karşılanamayan hemşirelik bakım öğelerinin ağız bakımı, banyo yaptırma ve yürütme (ambulasyon) gibi temel bakımla ilgili eylemler olduğu tespit edilmiştir. Genel olarak, hemşirelik personeli ve hastaların algıları hemşirelik bakımının belirli yönleri için benzer bulunmuştur.

Anahtar kelimeler: Karşılanamayan hemşirelik bakımı, hemşirelik bakımı, hemşirelik bakımı yönetimi, hasta bakımı, hasta güvenliği.

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INTRODUCTION

Patient care outcomes appear as a noteworthy indicator of the quality of care worldwide. It is evident that nurses play a significant role in achieving quality patient care outcomes[1], and all practices of nurses are considered within nursing care. A nursing care process can be assessed using several input variables (e.g., hospital type and staff characteristics) and output variables (e.g., patient falls, pressure ulcers, and infection rates) in the scope of quality measures.[2-3]

In patient safety, two fundamental error types are defined: error of commission - an error occurring when staff has made an action that they should not have done - (e.g., marking the wrong eye for surgery) and error of omission - an error occurring when staff has not done an action that they should have done (e.g., not providing patient ambulation).[4] Patient safety is deemed central to the nursing care process and is highly affected by both types of errors. While the error of commission receives substantial attention in the literature, it seems that the error of omission errors has not been adequately addressed.[5] Errors of omission can lead to undesirable consequences or adversely affect clinical outcomes. However, representing a bigger problem than errors of commission, errors or omission may become far more difficult to notice.[6,7]

A recently developed measure of the nursing care process is missed nursing care (MNC). MNC is an error of omission according to the patient safety literature.[5,8,9] The concept, which is considered a quality indicator of nursing care[10], was uttered for the first time by Kalisch[11] and defined as "*care that is delayed, partially completed, or not completed at all*".[5,11]MNC, linked with measuring how often and to what extent elements of nursing care are overlooked[2,3], is a unique form of medical error categorized as underuse.[1] The error inevitably brings adverse effects on the quality of nursing care and puts patient safety at risk.[12] Moreover, it not only affects the health of patients and nurses but also indirectly increases the number of days of hospital stay, pumping the cost of care services due to additional treatments.[13]

Considering the conceptual framework of MNC within Donabedian's concepts of structure, process, and outcome[11,14], while structure variables include hospital, patient care unit, and staff characteristics, the activities in providing and receiving care constitute process variables Then, "process" leads to MNC needs, affecting patient outcomes (e.g., falls, pressure ulcers, etc.) and staff outcomes (job satisfaction, burnout, intent to leave, etc.).[15]

Several studies exploring nurses' perceptions previously revealed that a substantial number of elements within nursing care are overlooked or significantly delayed.[2] Besides, the reasons why nurses cannot satisfy the required care were clustered under seven categories: too few staff, the time required for nursing intervention, poor use of existing staff resources, "not my job" syndrome, ineffective delegation, habits, and denial.[11] In their research, Kalisch et al. investigated the causes of MNC and concluded that the lack of labor resources appears as the most significant cause of MNC.[14] In the case of a poor number of employees, it is more likely that the remaining staff will not be able to complete all the required care. The lack of staff also causes the available staff to be unable to assist others in providing the necessary care, which leads to less care for each patient. For example, when a nurse cannot assist the patient in ambulating (due to the priorities of other patients), they are less likely to get help from another nurse to fulfill this need.[16]

There is a need to link certain aspects of nursing care to patient outcomes to help determine how necessary certain elements of nursing care are and how their completion affects the cost-benefit balance. Nursing care bears some elements that patients cannot evaluate; however, patient perspective on nursing care is considered essential to ensure appropriate and comprehensive nursing care.[2] Kalisch et al. previously grouped patients' ability to assess elements of nursing care into three categories: fully reportable, partially reportable, and non-reportable. In fully reportable areas, patients can report situations such as oral care, bathing, listening, briefing, call and alarm response, food assistance, pain relief, and follow-up, while partially reportable areas include care needs such as ambulation, patient education, medication management, repositioning, vital signs, and hand washing. Non-reportable areas, on the other hand, cover patient assessment, surveillance, and intravenous care.[2]

The literature demonstrates that necessary nursing care is sometimes overlooked for various reasons[1,3,9,17] which may imply that MNC is a global issue that should be brought under spotlights. However, the national literature in Türkiye hosts few research articles on MNC[3,12,18] , albeit more evidence is needed on this subject. In addition, the available studies often considered only the views of nurses on whether nursing care was completed or not. However, eliciting patient views on MNC may be as important as consulting nurses' views. Therefore, asking patients to report on their nursing care is likely to help empower them and increase their interest and participation in their own care. Moreover, identifying missed care interventions based on nurse and patient responses will pave the way for providing an objective assessment of and developing solutions to the reasons behind missed care needs.

The present study aimed to determine the levels of and the reasons for missed nursing care needs in a 505-bed state hospital in Türkiye based on nurse and patient responses.

MATERIAL AND METHODS

Research Questions

What is the amount and reasons for MNC needs from a nurse perspective in a public hospital in Türkiye?

What is the amount of MNC needs from a patient perspective in a public hospital in Türkiye?

Study Design

This cross-sectional regarding time dimension and descriptive in terms of purpose study was carried out with 172 nurses employed in the clinical divisions and 180 patients hospitalized in the clinical units of the relevant hospital between 15/11/-15/12/2019. The research included voluntary patients who were at least 18 years old, hospitalized for at least two nights, and not diagnosed with dementia, Alzheimer's disease, or any other psychiatric disorder. In addition the research included voluntary nurses who were at least 18 years old.

The number of nurses working in the hospital is 400.

The minimum sample size in the study was determined by performing power analysis with G*Power (v3.1.9.7) programme. Accordingly, the minimum sample size to be included in the study for 95% statistical test power (1-β) and 0.05 significance level (α) was calculated as at least 147 nurses. We tried to reach all of the nurses to increase the power of the study. The exclusion criteria of the study were nurses who were on leave or on report on the dates of the study and who did not accept to participate in the study. Three questionnaires were excluded due to incomplete responses to the distributed questionnaire forms. A total of 172 nurses' questionnaires were evaluated in the study.

Another research group in the study consisted of hospitalised patients. The sample of the research was determined by power analysis (G*Power). In the power analysis, the significance level (α)= 0.05 and the test power of the study (1-β) was taken as 0.95. In the power analysis, the type 1 error rate (α)= 0.05 and the power of the study (1-β) was taken as 0.95. As a result of the analysis, the sample size was calculated as 147 patient. On the dates of the study, an attempt was made to reach all patients who met the inclusion criteria of the study. Patients who did not meet the inclusion criteria and did not accept to participate in the study were excluded from the study. Ten questionnaires were excluded due to incomplete responses to the distributed questionnaire forms. A total of 180 patient questionnaires were evaluated in the study.

Data Collection Tools

The data were collected using two different questionnaires designed for nurses and patients.

The questionnaire administered to the nurses covered questions inquiring about the demographic characteristics of the nurses (12 items) and the Missed Nursing Care (MISSCARE) Survey (Part A 21 items and Part B 16 items). In the questionnaire applied to the patients, demographic characteristics of the patients (8 items) and MISSCARE-Patient (13 items) questions were included. The questionnaires were administered face-to-face to the participants. Prior to data collection, the authors, both holding the copyright of the surveys and adapting them in Turkish, were requested relevant permissions via e-mail.

MISSCARE Survey: Developed by Kalisch and Williams (2009) [8] and adapted into Turkish by Kalisch et al. (2012b) the survey is utilized to determine nurses' assessments of both the frequency and causes of missed care. [3] It consists of two parts. In the first part (Part A), the nursing staff is asked to rate how frequently each element is missed on a 5-point Likert-type scale ranging from "always missed" to "never missed." Part A consists of 21 items. In the second part (Part B), nurses are asked to state their views about the reasons for missed care in their units on a 4-point Likert-type scale ranging from "significant reason" to "not a reason for missed nursing care." Part B consists of 16 items. While interpreting the results, no score range indicates that the frequency of an investigated event is increasing or decreasing. Instead, higher scores in Part A show an increased frequency of missed nursing care, while higher scores in Part B indicate the importance of the reasons for missed nursing care. Reasons for not providing care are interpreted under three subscales: labor resources, material resources, and communication. In the first part of the scale (Part A), an increase in the score indicates an increase in the amount of missing nursing care needs, while an increase in the score in the second part (Part B) indicates the degree of importance of the reasons for missing nursing care needs.In the original study, Cronbach's α value for the first part of the scale was 0.93 and Cronbach's α value for the second part was 0.80. In this study, Cronbach's α value for the first part of the scale (Part A) was found to be 0.91, and Cronbach's α value for the second part of the scale (Part B) was found to be 0.86.

MISSCARE Survey-Patient: The MISSCARE Survey-Patient is a patient report survey assessing whether appropriate nursing care is provided. It was developed by Kalisch[11], tested for validity and reliability by Kalisch et al.[19](2014), and adapted into Turkish by Sönmez et al.[20](2020) The survey consists of 13 items related to the frequency and duration of nursing care interventions and three components: communication, timeliness, and primary care.[21] The communication component consists of five items, each scored on a 5-point Likert-type scale (1= never, 5= always), about how often the patient communicates with the nurse, whether they are informed about tests, procedures, treatment, and care, and whether their views are taken into account. The timeliness component includes four items; each scored between 1 (< 5 minutes) and 5 (> 30 minutes) and inquiring about the time elapsed before nurses respond to the need to urinate, the beeping monitor or machine, and the call signal or beep. Finally, the primary care component covers four questions about basic care needs (e.g., bathing, oral care, and transfer from bed to chair), scored on a 5-point Likert type scale (1 = never, 5 = always)[21]. Besides, two questions on the primary care component and four questions on the timeliness component included an additional response option to indicate that the patient does not need it (e.g., "I could not walk," "I never pushed my call button," etc.). Items in the communication and essential care components are reversely scored. The total score obtained from 13 items shows the total score of miss care. The Cronbach alpha internal consistency coefficient for the original scale[21] is 0.83. In the study conducted by Sönmez et al. [20] the Cronbach alpha internal consistency coefficient was 0.78.In this study, Cronbach's alpha coefficient of the scale was found to be 0.73.

Data Analysis

Descriptive statistics (frequency, percentage, mean, standard deviation, and minimum and maximum values) were presented to reveal the demographic characteristics of the participants and the levels of missed care. All analyses were performed on the SPSS 21.0 program.

Ethics Committee Approval

In order to carry out the research, research permission was obtained from the Chief Physician of Antalya Atatürk State Hospital with the letter numbered 7173619-619 and dated 15.10.2019. Ethics committee approval was obtained from the Clinical Research Ethics Committee of Antalya Training and Research Hospital (Date: 07.11.2019; Number:24/20). All nurses and patients participating in the study were informed

about the purpose of the study and the questionnaire, and after the necessary explanations were made, the consent of the nurses and patients who wanted to participate was obtained.

RESULTS

Descriptive Statistics of the Survey Scores

The mean and standard deviation values computed on the subscale and total scores are shown in Table 1. Considering the MISSCARE Survey-Patient, it was found out that the highest mean score was calculated on the primary care component (3.15 ± 1.22), while the lowest mean score belonged to the timeliness component (1.12 ± 0.90). The participants had a mean missed care score to be 2.05 ± 0.46. Considering the MISSCARE Survey, in contrast the participants got a mean score of 1.11±0.42 on Part A, it was 3.14 ± 0.50 on Part B.

The findings revealed that almost all (95.3%) nurses were females, 84.9% were married, and 80.2% had an undergraduate degree. The mean age of the nurses was 43 years. In addition, about half of them (41.9%) were deployed in surgical units, 69.8% worked in shifts, and 70.3% had a shift length of 24 hours. Most nurses (93%) claimed the number of nurses was insufficient, while 65.7% had moderate job satisfaction. Besides, 62.2% had no intent to leave the institution, while 70.9% had no intention to leave the profession. Considering the frequently confronted events in their units, 74.42% complained about prolonged hospitalization, 48.26% reported an increase in infectious diseases, and 31.40% claimed that the mortality rates increased.

Regarding the participating patients, 50.6% were women, and 78.9% were under 65. While 75% were hospitalized in surgical clinics, 85% had also been hospitalized. While 88.9% had a companion, 43.9% reported good health status. In addition, it was found that 27.8% were hospitalized with neurological diseases, 17.8% with heart diseases, 13.9% with bone diseases and ear, nose, and throat disorders, respectively, 13.3% with digestive disorders, 4.4% with kidney diseases, 3.9% with lung diseases, 3.3% with diabetes, and 1.7% with cancer.

Findings of MISSCARE Survey

Table 2 presents the nurse-reported frequencies of missed nursing care. Accordingly, the three most missed elements of nursing care were assisting the patient in ambulating three times per day or as ordered (6.4%), feeding the patient when the food is still warm (5.8%), and turning the patient every two hours (3.5%) (Table 2). Besides, the three sometimes/often missed elements of nursing care appeared as feeding the patient when the food is still warm (13.4% + 33.1%), patient bathing/skincare (18% + 9.9%), and assisting with toileting needs of the patient within five minutes of request (22.7% + 4.1%). Finally, the three least missed elements of nursing care (i.e., the most satisfied ones) became complete documentation of all necessary data (87.8%), patient assessments performed in each shift (86.6%), and hand washing (86%) (Table 2).

On the other hand, the nurses showed the inadequate number of staff (labor resources) (88.4%), supplies/equipment not functioning correctly (material resources) (62.8%). Other departments' not providing the care needed (communication) (59.9%) as the most significant reasons for missed care (Table 3).

Findings of MISSCARE Survey-Patient

The patient-reported proportions of missed nursing care are given in Tables 4 and 5. Accordingly, it was found that the three most missed elements of nursing care were covered in the primary care component: oral care (31.7%), bathing (28.9%), and ambulation (18.3%). On the other hand, the three least missed elements of nursing care (i.e., the most satisfied ones) appeared in the communication component: providing information about tests/procedures (47.8%), talking to the patient about the treatment/care (35.0%), and the nurse's introducing themselves to the patient (31.7%) (Table 4).

The timeliness component consists of items inquiring about the time elapsed before nurses respond to the patient's needs. The patients reported the following happened within 5-10 minutes on average: the nurse responded when a monitor or other machine beeped (25.1%), the nurse responded to the call light (37.2%), the patient got help when the call light was answered (37.2%), and the nurse arrived when the patient needed to go to the bathroom (37.2%) (Table 5).

When the rates of adverse events reported by the patients in the last part of the misscare survey-patient were examined, patients stated that they experienced subcutaneous leakage from the vascular (26.1%), vascular occlusion (23.3%), development of new infections (14.4%) and deterioration of skin integrity/bed sores (10%). Most patients stated that they did not experience falls or medication errors (Table 6).

DISCUSSION

Missed nursing care is considered a multidimensional

Table 1. Descriptive statistics of scales

Scales and Subscale	Number of Items	Min	Mak	$\bar{X}$	SD
Misscare Survey-A	**21**	0.10	3.05	1.1099	0.41772
Misscare Survey-B	**16**	1.00	4.00	3.1395	0.49662
Labor resources	4	1.00	4.00	3.5131	0.53617
Communication	9	.00	3.00	1.0336	0.38399
Material resources	3	1.00	4.00	3.4225	0.67907
	Number of Items	**Min**	**Mak**	$\bar{X}$	**SD**
Misscare Survey -Patient	**13**	**0.85**	**3.08**	**2.0555**	**0.46828**
Communication	5	1.00	3.40	1.9067	0.52772
Basic care	4	0.50	5.00	3.1542	1.22197
Timeliness	4	0.00	3.00	1.1222	0.90324

Source: The authors.
Note: Min: Minimum, Max: Maximum, $\bar{X}$: Average; SD: Standard deviation

Table 2. The nurse-reported frequencies of missed nursing care

	Never missed	Rarely missed	Sometimes missed	Often missed	Always missed
	n (%)	n (%)	n (%)	n (%)	n (%)
Ambulation three times per day or as ordered	42 (24.4)	91 (52.9)	10 (5.8)	18 (10.5)	**11 (6.4)**
Turning patient every 2 hours	41 (23.8)	92 (53.5)	10 (5.8)	23 (13.4)	**6 (3.5)**
Feeding patient when the food is still warm	20 (11.6)	62 (36.0)	**23 (13.4)**	**57 (33.1)**	**10 (5.8)**
Setting up meals for patients who feed themselves	31 (18.0)	127 (73.8)	8 (4.7)	5 (2.9)	1(0.6)
Medications administered within 30 minutes before or after scheduled time	13 (7.6)	145 (84.3)	7 (4.1)	6 (3.5)	1 (0.6)
Vital signs assessed as ordered	19 (11.0)	142 (82.6)	7 (4.1)	4 (2.3)	0
Monitoring intake/output	14 (8.1)	146 (84.9)	8 (4.7)	4 (2.3)	0
Complete documentation of all necessary data	10 (5.8)	**151 (87.8)**	8 (4.7)	3 (1.7)	0
Patient teaching about procedures, tests, and other diagnostic studies	12 (7.0)	146 (84.9)	6 (3.5)	7 (4.1)	1 (0.6)
Emotional support to patient and family	9 (5.2)	141 (82.0)	13 (7.6)	6 (3.5)	3 (1.7)
Patient bathing/skin care	40 (23.3)	79 (45.9)	**31 (18.0)**	**17 (9.9)**	5 (2.9)
Mouth care	21 (12.2)	119 (69.2)	18 (10.5)	11 (6.4)	3 (1.7)
Handwashing	15 (8.7)	**148 (86.0)**	6 (3.5)	3 (1.7)	0
Teach the patient about plans for their care after discharge and when to call after discharge	19 (11.0)	140 (81.4)	8 (4.7)	4 (2.3)	1 (0.6)
Bedside glucose monitoring as ordered	13 (7.6)	147 (85.5)	8 (4.7)	4 (2.3)	0
Patient assessments performed each shift	12 (7.0)	**149 (86.6)**	6 (3.5)	5 (2.9)	0
IV/central line site care and assessments according to hospital policy	12 (7.0)	147 (85.5)	7 (4.1)	6 (3.5)	0
Response to call light is initiated within 5 minutes	26 (15.1)	116 (67.4)	24 (14.0)	6 (3.5)	0
PRN medication requests were acted on within 15 minutes	15 (8.7)	136 (79.1)	15 (8.7)	5 (2.9)	1 (0.6)
Assess the effectiveness of medications	21 (12.2)	133 (77.3)	8 (4.7)	9 (5.2)	1 (0.6)
Assist with toileting needs within 5 minutes of request	29 (16.9)	94 (54.7)	**39 (22.7)**	7 (4.1)	3 (1.7)

Source: The authors.
Note: n=Number **; %=**Percentage

Table 3. The nurse-reported frequencies of reasons for missed nursing care

	Significant a reason	Moderately important reason	Little a reason	Not a reason for missed nursing care
Labor Resources	n (%)	n (%)	n (%)	n (%)
(Level of staffing) Inadequate number of staff	**152 (88.4)**	13 (7.6)	4 (2.3)	3 (1.7)
Urgent patient situations (e.g., a patient's condition worsening)	107 (62.2)	51 (29.7)	8 (4.7)	6 (3.5)
Unexpected rise in patient volume and acuity in the unit	85 (49.4)	63 (36.6)	20 (11.6)	4 (2.3)
Inadequate number of assistive personnel (e.g., nursing assistants, techs, unit secretaries, etc.)	84 (48.8)	76 (44.2)	7 (4.1)	5 (2.9)
Communication				
The high number of inexperienced personnel in the service	61 (35.5)	82 (47.7)	22(12.8)	7 (4.1)
(The method of making patient assignments) Unbalanced patient assignments	48 (27.9)	61 (35.5)	48 (27.9)	15 (8.7)
Inadequate handoff from the previous shift or sending unit	78 (45.3)	60 (34.9)	26 (15.1)	8 (4.7)
Other departments did not provide the care needed (e.g., physical therapy did not ambulate)	**103 (59.9)**	41 (23.8)	22 (12.8)	6 (3.5)
Lack of backup support from team members	62 (36.0)	57 (33.1)	45 (26.2)	8 (4.7)
Tension or communication breakdowns with other ancillary/ support departments	44 (25.6)	48 (27.9)	63 (36.6)	17 (9.9)
Tension or communication breakdowns within the nursing team	42 (24.4)	52 (30.2)	54 (31.4)	24 (14.0)
Tension or communication breakdowns with the medical staff	47 (27.3)	43 (25.0)	59 (34.3)	23 (13.4)
The nurse leaving the service for any reason other than the nursing care service or not being able to reach their	44 (25.6)	29 (16.9)	37 (21.5)	62 (36.0)
Material Resources				
Medications not available when needed	89 (51.7)	59 (34.3)	19 (11.0)	5 (2.9)
Supplies/equipment not available when needed	99 (57.6)	53 (30.8)	13 (7.6)	7 (4.1)
Supplies/equipment not functioning correctly when needed	**108 (62.8)**	46 (26.7)	14 (8.1)	4 (2.3)

Source: The authors.
Note: n=Number **; %=**Percentage

Table 4. The patient-reported frequencies of missed nursing care (communication and primary care)

	Always (not missed nursing care)	Usually	Sometimes	Rarely	Never
Communication	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
How often do you know who the nurse assigned to look after you on the shift is?	57 (31.7)	99 (55.0)	20 (11.1)	2 (1.1)	2 (1.1)
How often did your nurse talk to you about your treatment and care?	63 (35.0)	94 (52.2)	22 (12.2)	1 (0.6)	0
How often did your nurse inform you about the tests and procedures performed during your hospitalization?	86 (47.8)	78 (43.3)	14 (7.8)	2 (1.1)	0
Did your nurse listen to you when you had a question or concern about your care or illness?	48 (26.7)	85 (47.1)	39 (21.7)	5 (2.8)	3 (1.7)
When you had an opinion or idea about what needs to be done about your care, did the nurse take these views and ideas into account?	38 (21.1)	75 (41.7)	53 (29.3)	10 (5.6)	4 (2.3)
Basic care	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
How often did the nurse check if you brushed your teeth and rinsed your mouth (or how often did the nurse do your oral care if you couldn't do this)?	9 (5.0)	13 (7.2)	50 (27.8)	51 (28.3)	**57 (31.7)**
During your hospital stay, how often did the nurse check on you to make sure you were taking a bath or that your body was clean?	13 (7.2)	26 (14.4)	46 (25.6)	43 (23.9)	**52 (28.9)**
*On average, how often did the nurse assist or watch you get out of bed and sit in a chair?	29 (16.1)	17 (9.4)	43 (23.9)	35 (19.4)	32 (17.8)
*On average, how often did the nurse assist or monitor your walking?	41 (22.8)	16 (8.9)	36 (20.0)	31 (17.2)	**33 (18.3)**

* In the last two items with a sixth response option in the primary care subscale, 13.3% of the participants reported being unable to get out of bed, and 12.8% unable to walk.
Source: The authors.
Note: n=Number **; %=**Percentage

Table 5. The patient-reported frequencies of missed nursing care (timeliness)

Timeliness	No Machine Beeps	< 5 minutes	5 -10 minutes	11 - 20 minutes	21 - 30 minutes	> 30 minutes
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
When a monitor or other machine beeped, how long did it usually take for the nurse to intervene?	105 (58.3)	15 (8.3)	45 (25.1)	13 (7.2)	2 (1.1)	0
When you pressed your call light/ bell (or called the nurse), how long, on average, did it take the nurse to respond?	59 (32.8)	21 (11.7)	67 (37.2)	30 (16.17)	1 (0.6)	2 (1.1)
Once your call light/bell (or call) was answered, how long on average did it take you to get the help you wanted?	58 (32.2)	23 (12.8)	67 (37.2)	29 (16.1)	3 (1.7)	0
When you needed help going to the toilet, how long did it take for the nurse to come to your room to help?	104 (57.7)	18 (10.0)	45 (25.1)	11 (6.1)	2 (1.1)	0

Source: The authors.
Note: n=Number**; %=**Percentage

Table 6. Findings on patient-reported adverse events

Adverse Events	Yes	No	I'm not sure
	n (%)	**n (%)**	**n (%)**
Fall	0	153 (%85)	27 (%15)
Deterioration of skin integrity / Bed sores	18 (%10)	135 (%75)	27 (%14.4)
Medication errors	0	145 (%80.6)	35 (%19.4
Development of new infections	26 (%14.4)	111 (%61.7)	43 (%23.9)
Vascular occlusion	42 (%23.3)	95 (%52.8)	43 (%23.9)
Subcutaneous leakage from the vascular	47 (%26.1)	88 (%48.9)	45 (%25)

Source: The authors.
Note: n=Number **; %=**Percentage

construct; thus, the nursing profession must demonstrate a multifaceted response to address it.[22] Besides, patients, as well as nurses, can be decisive in missed nursing care. Further research is needed to investigate how patients perceive missed care to suggest a more comprehensive definition of the concept.[23] The present research was carried out to determine missed nursing care in a state hospital based on the perceptions of nurses and patients.

Based on the participating nurses' responses, the findings revealed the three most missed elements of nursing care: assisting the patient in ambulating three times per day or as ordered, feeding the patient when the food is still warm, and turning the patient every two hours. In addition, patient bathing/skincare, and assisting with toileting needs of the patient within five minutes of the request were found to be the elements of sometimes/often missed nursing care. Özdelikara and Yaman conducted a study to reveal the health anxiety and frequencies and causes of missed nursing care among nurses deployed during the pandemic.[24] The participating nurses indicated assisting the patient in ambulating three times per day or as ordered (23.5%), turning the patient every two hours (20%), and patient bathing/skincare (19.5%) as the most missed elements of nursing care. In their study in a university hospital, İlaslan and Şişman concluded that the most missed elements of nursing care are ambulating three times per day or as ordered, providing emotional support to patient and family, and attending interdisciplinary care conferences whenever held.[12] In addition, Palese et al. found patient ambulation (91.4%), turning the patient every two hours (74.2%), and medication at the right time (64.6%) to be frequently missed practices.[7] Ultimately, the findings in this study and the literature overlap, concluding that the nurses reported the most missed care element to be patient ambulation, that is, assisting the patient in ambulating three times per day or as ordered. Similarly, the literature host other studies revealing ambulation to be the most missed element of nursing care.[3,14,18,25-27]

According to the participating nurses, the most apparent reasons for missed nursing care were the inadequate number of staff (labor resources) (88.4%), supplies/ equipment not functioning correctly (material resources) (62.8%), and other departments' not providing the care needed (communication) (59.9%). Similarly, in different studies in Türkiye, the participating nurses reported the inadequacy of the number of staff as the most crucial reason for missed nursing care.[12,24] Saqer and Abu Al Rub reported that the most common cause for missed nursing care be related to labor resources.[28] According to 2019 OECD data, the average number of nurses per 1,000 people in OECD countries was about 8.85. Yet, Türkiye ranks as the last country on the list with an average number of 2.4 nurses per 1,000 people.[29] While the OECD average for the ratio of physicians to nurses was 2.6, this ratio became 1.2 in Türkiye in 2019. The relevant OECD statistics indicate the insufficient number of nurses in Türkiye and their excessive workload. The same story applies to nursing education. The average number of nursing graduates per 100,000 people was 44.5 for OECD countries, albeit it was 18.7 for Türkiye[30], which implies that the problem of the insufficient number of staff is not likely to be eliminated shortly.

The relevant research in the literature often linked missed nursing care to complicated registration systems and technical procedures in the management of nursing care, the insufficient number of staff, and intensive patient admission and discharge procedures.[3,9,17,31-33] Thus, it can confidently be asserted that the present findings overlap the literature regarding insufficient staff.

When it comes to missed nursing care from the patient's perspective, the findings revealed the most missed elements of nursing care to be related to primary care: oral care, bathing, and ambulation. In the study of Kalisch et al. the five most missed elements of nursing care were reported to be oral care, ambulation, assisting the patient in getting out of bed and sitting on a chair, informing the patient about tests/procedures, and bathing.[19] Besides, the participating patients reported missed nursing care within primary care rather than communication and timeliness. In their research, Gustafsson et al. found that patients reported problems with primary care, communication, and timeliness, respectively.[23]

In this study, the patients also reported adverse events to be intravenous (IV) leakage in their skin (26.1%), IV occlusions (23.3%), new infection (14.4%), and skin breakdown/pressure ulcer (10%). The fact that IV leakage in the skin and IV occlusion were among the most frequently reported adverse events overlaps the findings in previous research.[19,20,34] Nevertheless, the patients did not report falls or medication administration errors, unlike the findings in other studies.[19,34]It is thought that the reasons uttered for missed nursing care (e.g., the insufficient number of staff, communication, and teamwork) may have caused the mentioned adverse events. Indeed, there were patient reports that more nurses provide a faster response to patient needs.[21] Gustafsson et al. concluded that patient-reported adverse events were associated with patients' perceptions of staff competence and that a perceived lack of staff and inadequate staff experience might lead to missed care.[23]

CONCLUSION

This study aimed to determine the perspectives of nurses and patients towards investigating missed nursing care. Accordingly, it was found that ambulation, feeding the patient while the food was still warm, and turning the patient every two hours became the most missed elements of nursing care. From the patient's perspective, it was determined that the most missed elements of nursing care were related to primary care (e.g., oral care, bathing, and ambulation). Overall, perceptions of nursing staff and patients were similar for certain aspects of nursing care. Besides, it is noteworthy that the nurses showed the insufficient number of staff as the most significant reason for missed nursing care. Furthermore, the patients reported experiencing IV leakage in their skin, IV occlusion, new infections, and skin breakdown/pressure ulcers. In line with these results, it is recommended to make necessary arrangements (adequate number of personnel, etc.) with manpower planning based on scientific basis for the working conditions of nurses, and to increase and support training opportunities and in-service training pro-

grammes. In addition, further research is recommended to recruit the views and perceptions of nurses and patient on missed nursing care.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Antalya Training and Research Hospital (Date: 07.11.2019, Number: 24/20).
Informed Consent: Written and/or verbal consent was obtained from patients and nurses participating in the study.
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PERCEIVED EXERCISE BELIEFS AND BARRIERS AMONG BREAST CANCER SURVIVORS: A DESCRIPTIVE CROSS-SECTIONAL STUDY
MEME KANSERİ SAĞKALIMLARINDA ALGILANAN EGZERSİZ İNANIŞLARI VE ENGELLERİ: TANIMLAYICI KESİTSEL BİR ARAŞTIRMA

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ABSTRACT

Since the importance of the benefit of physical activity and exercise has been understood especially for cancer patients, efforts are taken to assess belief in exercise to adapt patients to a more physically active environment to create a sustainable health outcome. Thus, this study aimed to assess exercise beliefs and barriers by using a validated metric tool (Exercise Beliefs/Barriers Scale-EBBS) to evaluate beliefs in exercise in breast cancer survivors (BCS). In addition, it was also aimed to assess the relationships among EBBS, sociodemographic, and clinical variables of BCS. A total of 112 BCS were screened and invited to participate in this study. Clinical (type of surgery, adjuvant treatments, etc.), demographic data (age, medication use, etc.), and total sitting time were collected through a simple data form and 7th of the International Physical Activity Questionnaire-Short Form (IPAQ-SF), respectively. All patients were requested to fill out EBBS.96 BCS completed this study. Weak but significant correlations were found between time spent after surgery and perceived belief (r=. -273, p=0.009), and perceived barriers (r=-.239, p=0.022), respectively. Perceived barriers were also significantly correlated with age (r=-.212, p=0.042). No significant effects of the type of breast surgery and axillary procedure as well as medications (Tamoxifen) on perceived beliefs and barriers were found. Factors should be thoroughly investigated to provide a sustainable exercise behavior among BCS. Older BCS should be thoroughly monitored to gain regular exercise behavior. This study also highlighted the emerging need for sensitive, specific, and focused tools to assess beliefs in exercise among the cancer population.

Keywords: Breast cancer, exercise, exercise barriers, exercise beliefs, physical inactivity .

ÖZ

Özellikle kanser hastaları için fiziksel aktivite ve egzersizin faydasının önemi anlaşıldığından, sürdürülebilir bir sağlık sonucu yaratmak için hastaları fiziksel olarak daha aktif bir ortama adapte etmek amacıyla egzersize olan inancı değerlendirmek için çaba gösterilmektedir. Bu nedenle, bu çalışma meme kanserinden kurtulanlarda egzersize olan inancı değerlendirmek için geçerliliği kanıtlanmış bir ölçme aracı (Egzersiz İnançları/Engelleri Ölçeği-EBBS) kullanarak egzersizin faydalarını ve engellerini değerlendirmeyi amaçlamıştır. Ayrıca, EBBS ile hastaların sosyodemografik ve klinik değişkenleri arasındaki ilişkilerin değerlendirilmesi de amaçlanmıştır. Toplam 112 hasta taranmış ve bu çalışmaya katılmaya davet edilmiştir. Klinik (ameliyat tipi, adjuvan tedaviler, vb.), demografik veriler (yaş, ilaç kullanımı, vb.) ve toplam oturma süresi sırasıyla basit bir veri formu ve Uluslararası Fiziksel Aktivite Anketi-Kısa Formunun (IPAQ-SF) 7. maddesi aracılığıyla toplanmıştır. Tüm hastalardan EBBS'yi doldurmaları istenmiştir. 96 hasta bu çalışmayı tamamlamıştır. Ameliyat sonrası geçirilen süre ile algılanan inanç (r=.-273, p=0.009) ve algılanan engeller (r=-.239, p=0.022) arasında anlamlı korelasyonlar bulunmuştur. Algılanan engeller yaş ile de anlamlı şekilde ilişkiliydi (r=-.212, p=0.042). Meme cerrahisi tipi ve aksiller prosedür tipinin yanı sıra ilaçların (Tamoksifen) algılanan inançlar ve engeller üzerinde anlamlı bir etkisi bulunmamıştır. Hastalar arasında sürdürülebilir bir egzersiz davranışı sağlamak için faktörler kapsamlı bir şekilde araştırılmalıdır. Yaşlı hastalar düzenli egzersiz davranışı kazanmak için kapsamlı bir şekilde izlenmelidir. Bu çalışma aynı zamanda kanser popülasyonu arasında egzersize yönelik inançları değerlendirmek için hassas, spesifik ve odaklanmış araçlara duyulan ihtiyacın altını çizmiştir.

Anahtar kelimeler: Meme kanseri, egzersiz, egzersiz engelleri, egzersiz inanışları, fiziksel inaktivite.

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INTRODUCTION

Breast cancer (BC) is the most frequent type of cancer among women globally. The incidence of BC was reported to be 13%.[1] 2.3 million new female BC cases (11.7%) were reported as the leading type of cancer among women according to the GLOBOCAN data.[2] However, thanks to the advancements in screening, awareness, and treatment options in BC as well as early detection of BC lead to prolonged disease-free survival rates of up to nearly 80% for fifteen years.[3]

Breast cancer survivors (BCS) face many challenges through different aspects of survivorship issues in a wide variety of aspects from fat gain, bone and muscle loss, neuropathy, myalgia, arthralgia, and breast cancer-related lymphedema[4-6]. Therefore, there is a growing need to pay attention to manage of short and long-term side effects of the treatment of BC. Not only for the purpose of improving clinical outcomes and quality of life of BCS but also for optimizing the health care costs of BCS have been understood to be the key factors in the long term.[7] For instance, the estimated healthcare costs of BCS are above 20 billion $ in the care of BCS in which chronic care takes the lion's share.[8] Rashid et al.[9] also stated that nearly six hundred million dollars are spent on the treatment-related side effects of musculoskeletal problems among BCS.

There is a growing body of evidence that exercise plays a vital role in preventing side effects of BC treatment as well as improving treatment efficacy among BCS. Numerous positive effects of exercise on increased cardiopulmonary and functional capacity, muscle strength, self -esteem, and decreased fatigue have been well-known facts among BCS.[10, 11] In addition, it is a well-recognized fact that exercise has significant positive effects on anxiety, depression as well as sleep disorders in patients with breast cancer.[12-15] Although there is a high level of evidence as well as its proven safety and feasibility of exercise among BCS not only during the active treatment period but also afterward, the rate of meeting exercise recommendations according to the guidelines is dramatically low among BCS. To establish an improved continuity of care for BCS, a need for sustainable and regular physical activity and exercise habits is indisputable. Yet, there are lots of points underpinned that decreased participation in exercise and unsustainable physical activity among BCS are not only associated with treatment-related side effects but also other issues that should be thoroughly addressed.[16-19] Understanding the major factors that might play a role in decreased physical activity may create an efficient way toward achievable and sustainable exercise habits.

There are numerous studies associated with perceived exercise barriers and beliefs among cancer survivors. Yet, most of the studies solely rely on its qualitative nature instead of a quantitative design. There is an emerging need for studies in which perceived exercise barriers and beliefs are assessed and analyzed quantitatively. Therefore, we aimed to analyze perceived exercise beliefs and barriers among BCS as well as analyze their relationships with the clinical characteristics of BCS in this study. Our hypotheses were based on that age, time spent after primary treatment, and body mass index (BMI) would show significant relationships with perceived exercise beliefs and barriers.

MATERIALS AND METHODS

Study Design

This observational study was planned as a cross-sectional study and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[20] A non-probability sampling method was used. This study was held between December 2019 and April 2021. All procedures and measurements were performed according to the 1964 Helsinki Declaration and approval was granted by the Ethics Committee of the University of Health Sciences with the protocol number 11092019/02. All participants were informed before the enrollment of this study and written informed consent was taken.

Patients

Patients with BC were screened and invited to participate in this study. Aged over 18 years old, female gender, having completed their primary treatments (surgery, chemotherapy, and radiotherapy), and volunteered to participate in this study were set as inclusion criteria. Having mental/cognitive disorder (s), undergoing active chemotherapy and/or radiotherapy, and having orthopedic and/or neurological conditions and/or mild to moderate co morbidities that might impede engaging in exercise were set as exclusion criteria.

Assessment

Demographic data form

The patients' clinical and socio-demographic data (age, BMI, type of surgery, axillary procedure, history of chemotherapy and/or radiotherapy, time spent after surgery (TSS), and medications) was gathered via a simple data form.

Physical inactivity level

Patients' physical inactivity level was assessed with the 7th question of the Turkish version of the International Physical Activity Questionnaire-Short Form (IPAQ-SF)[21] which evaluates the mean sitting time of the last seven days of respondents. The patients were asked to fill out only the 7th question of IPAQ-SF instead of the whole questionnaire.

Perceived exercise beliefs and barriers

Patients' perceived exercise beliefs and barriers was assessed with the Exercise Benefits/Barriers Scale (EBBS). The original version of the EBBS was developed by Sechrist et al.[22] in 1987. EBBS consists of a total of 43 items in which a total of 29 items assess perceived exercise benefits while the rest of 14 items assess perceived exercise barriers in a four-point Likert type scale from "Strongly disagree:1:" through "Strongly disagree:4". Scores can be used to depict perceived barriers (range 14-56), perceived benefits (range 29-116), or total score (range 43-156). However, many studies have used its core sub-features according to the exploratory factor analysis as follows: Life Enhancement (LE), Physical Performance (PP), Psychological Outlook (PO), Social Interaction (SI), and Preventive Health (PH) can be used to depict exercise beliefs, whereas Exercise Milieu (EM), Time Expenditure (TE), Physical Exertion (PE), and Family Discouragement (FD) can be used to depict perceived exercise barriers. Higher scores indicate a positive attitude toward perceived beliefs or barriers to exercise or vice versa.

Statistical analysis

The data were reported as means and standard devia-

tion, median and interquartile range (IQR), or number and percentage depending on the type of data, whether continuous or categorical. Normality was assessed with Kolmogorov Smirnov-Shapiro Wilk tests as well as skewness and kurtosis. If the assumptions of normality were met, independent samples t-tests or in case of violation of normal distribution, Mann-Whitney U tests were used to analyze the data in two different groups such as between patients who underwent MRM or BCS or between patients who underwent ALND or SLNB. Bivariate correlations were analyzed according to the normality assumptions and presented by Pearson's r or Spearman's rho correlation coefficients according to the normal distribution and non-normal distribution, respectively. Correlation coefficients are interpreted as follows: r<.20 poor, .21<r<.40 fair, .41<r<.60 moderate, .61<r<.80 good and .81<r<.1 excellent.[23]Missing data were handled with the mean of nearby points. The p-value below .05 was accepted as statistically significant. Statistical analysis was performed with IBM SPSS v.20 (IBM Corp, NY).

RESULTS

A total of 112 BCS were screened to participate in this study. 16 BCS were excluded due to several reasons according to the predefined inclusion and exclusion criteria. A detailed participation process is shown in Figure 1 as a flow chart.

96 BCS (Mean age and BMI: 52.00±10.05 years and 27.77±3.75 kg/m^2) fulfilled all assessments. A total of 5 patients' (5.2%) weight and/or height data could not be retrieved from the data form, therefore, the median of nearby points was used to replace the missing data for further analysis. The mean TSS was 2.32±1.74 (min-max 0.5-9.75) years. After categorization, above half the half of the BCS' time spent after surgery (54 out of 96 BC patients, 56.3 %) was between 1 and 3 years. The detailed clinical characteristics of patients are shown in Table 1.

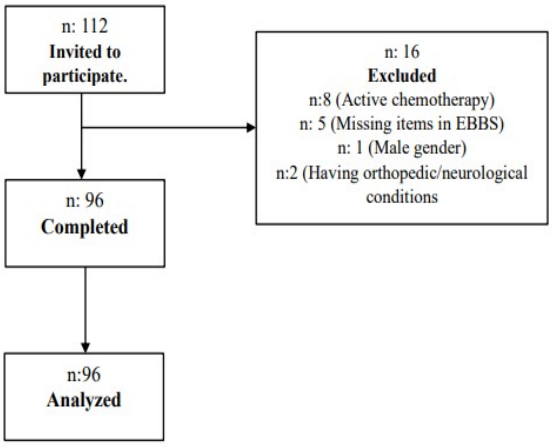

Figure.1 Flow chart of the study participation process.

Table 1: Clinical and sociodemographic characteristics of patients

Characteristics n=96	Min	Max	Mean (SD)
Age (years)	33	76	52.00±10.05
BMI (kg/m^2)	19.96	38.01	27.77±3.75
Time spent after surgery (years)	0.5	9.75	2.32±1.74
Time spent after surgery	**n**	**%**	
0-1 year	21	21.8	
1-3 years	54	56.3	
3-5 years	14	14.6	
5 years or more	7	7.3	
Marital Status			
Married	84	87.5	
Single/divorced	12	12.5	
Type of Surgery			
Conservative	68	70.8	
MRM	28	29.2	
Type of axillary procedure			
SLNB	16	16.7	
ALND	80	83.3	
Grade			
1	23	23.9	
2	47	48.9	
3	25	26.1	
4	1	1.1	
History of chemotherapy			
Yes	82	85.4	
No	14	14.6	
History of radiotherapy			
Yes	92	95.8	
No	4	4.2	
Tamoxifen use			
Yes	44	45.8	
No	52	54.2	
Aromatase Inhibitor use			
Yes	43	44.8	
No	53	55.2	

SD: Standard deviation, **BMI**: Body mass index, **MRM**: Modified radical mastectomy, **SLNB**: Sentinel lymph node biopsy, **ALND**: Axillary lymph node dissection

The mean scores of perceived exercise benefits and barriers as well as sub dimensions of EBBS, and total sitting time are shown in Table 2. The median value of the perceived barriers and benefits scale were found as 33.5 (31-36) and 90(88-93.75) respectively. The details of the scores of EBBS and its sub-dimensions as well as the mean sitting time are shown in Table 2.

Table 2. The detailed mean scores of sitting time and perceived exercise barriers and benefits of patients.

Characteristics n=96	Min	Max	Median (IQR$^{25-75}$)
Sitting time (hrs)	1	12	5.68 (4-6)
	EBBS		
	Min	**Max**	**Median (IQR$^{25-75}$)**
Perceived benefits (range)	70	121	90 (88-93.75)
LE (8-32)	17	32	27 (26-27)
PP (8-32)	18	28	21 (21-21.75)
PO (6-24)	11	24	18 (17-19)
SI (4-16)	4	15	11 (9-12)
PH (3-12)	6	12	9 (8-9)
	Min	**Max**	**Median (IQR$^{25-75}$)**
Perceived barriers (range)	22	46	33.5 (31-36)
EM (6-24)	12	24	17 (15.25-18)
TE (3-12)	5	12	9 (9-9)
PE (3-12)	3	11	8 (7-9)
FD (2-8)	3	8	6 (4-6)

Hrs: Hours, **SD**: Standard deviation, LE: Life enhancement, **PP**:Physical performance, **PO**: Psychological outlook, **SI**: Social interaction, **PH**: Preventive health, **EM**: Exercise milieu, **TE**: Time expenditure, **PE**: Physical exertion, **FD**: Family discouragement, **IQR**: Interquartile range, **Min**: Minimum, **Max**: Maximum

When it comes to relationships between parameters, perceived exercise benefits subscales (LE, PP, PO, SI, and PH) were found to be significantly correlated from mild through higher levels in each other (data not shown). The same pattern was also observed in between some parameters of perceived exercise barriers subscales. The physical inactivity, as assessed via the 7th question of IPAQ-SF in which mean sitting time on a day was requested as hours or minutes, was not found to significantly correlate with all parameters of EBBS as well as other clinical and sociodemographic variables. Yet, there was a significant positive correlation between age and total sitting time at a fair level (r=.258, p=0.017). The TSS was also found to be significantly and negatively correlated fairly with PP (r=-.273, p=0.009), EM (r=-.239, p=0.022), and age (r=.349, p<0.001). TSS was also significantly correlated fairly with the type of surgery (r=.266, p=0.009), type of axillary procedure (r= -.209, p=0.041), history of RT (r=.224, p=0.028), and history of aromatase inhibitor use (r=.374, p<0.001) in point biserial correlations. Age had also a significant negative correlation with a history of tamoxifen use (r=. -497, p<0.001) and a history of aromatase inhibitor use (r=.438, p<0.001) in moderate levels. Details of correlation analyses among sociodemographic and clinical variables and subscales of EBBS are also shown in Table 3.

Although there were differences in the mean scores of the subscales of perceived beliefs and barriers between groups (MRM vs. conservative surgery; and ALND vsSLNB), these differences did not reach significance (p>.05).

DISCUSSION

This study showed relatively acceptable and expectable levels of perceived exercise beliefs and barriers among BCS. Our findings are in parallel with the literature findings.[6,24] Notably, prolonged time spent after surgery was also noteworthy to take into consideration its effect on physical function and exercise milieu both in perceived exercise beliefs and barriers, respectively. Contrary to expected, the level of physical inactivity was not found to correlate significantly with any of the subscales as well as other clinical and sociodemographic characteristics of patients except for fairly with age. However, the main reason for this insignificant result might have originated from the assessment of physical activity only with a single question which directly covers total sitting time in a day.

Exercise has been reported to be the greatest option to manage short- and long-term consequences of treatment-related side effects such as fatigue,[25,26] anxiety,[12,15] cancer related cognitive impairment,[27] and cardiotoxicity[28] among cancer patients during treatment and chronic care. Despite the benefits of exercise being well known, adherence to exercise and/or physical activity is dramatically low among BCS according to the recommended level of weekly dosage of a minimum of 150 minutes of moderate physical activity.[29] It was also reported that nearly half of Taiwanese BC survivors did not exercise at all.[17]Chan et al.[30] reported that patients significantly lowered their physical activity level following the diagnosis of cancer. Notably, cancer itself does not impede adherence to physical activity since comparative studies showed that there is no significant difference between patients with and without cancer.[31] Although we assessed the patients' physical inactivity level by gathering total sitting time, it was seen that there was no regular exercise habit among our patients. We tried to use the mean total sitting time as physical inactivity level instead of physical activity. Although there is no report on whether physical activity and inactivity can be used interchangeably, assessment of physical inactivity usually focuses on "sitting time" during daily life. For instance, nearly half of the items of the Turkish version of the Sedentary Behavior Questionnaire (SBQ)[32] assesses physical inactivity by using the

Table 3. Correlations between subscales of EBBS and clinical-sociodemographic characteristics of patients

	Perceived Benefits					Perceived Barriers			
n=96	**LE**	**PP**	**PO**	**SI**	**PH**	**EM**	**TE**	**PE**	**FD**
Age	r=.155 **p=.14**	r=.079 **p=.45**	r<0.01 **p=.99**	r=.117 **p=.26**	r=.116 **p=.27**	r=. -212 ***p=0.042**	r=-.018 **p=.86**	r=-.005 **p=.96**	r=.109 **p=.30**
BMI	r=.093 **p=.38**	r=-.040 **p=.70**	r=-.022 **p=.83**	r=.119 **p=.25**	r=.137 **p=.19**	r=-.037 **p=.72**	r=.035 **p=.74**	r=.129 **p=.22**	r=.265 ***p=0.011**
Sitting Time	r=-.070 **p=.50**	r=.001 **p=.99**	r=**.052** **p=.62**	r=-.003 **p=.97**	r=-.145 **p=.16**	r=.082 **p=.43**	r=-.053 **p=.61**	r=.059 **p=.57**	r=.078 **p=.45**
Type of surgery	r=.049 **p=.64**	r=-.031 **p=.77**	r=-.059 **p=.58**	r=.057 **p=.59**	r=.030 **p=.77**	r=-.124 **p=.23**	r=-.066 **p=.53**	r=.012 **p=.91**	r=-.028 **p=.79**
Type of axillary procedure	r=-.132 **p=.21**	r=-.026 **p=.80**	r=-.011 **p=.91**	r=-.193 **p=.06**	r=-.097 **p=.35**	r=-.006 **p=.95**	r=-.023 **p=.83**	r=.004 **p=.97**	r=-.149 **p=.15**
History of radiotherapy	r=.204 **p=.051**	r=.110 **p=.29**	r=.233 ***p=0.025**	r=.112 **p=.28**	r=.238 ***p=0.022**	r=-.018 **p=.86**	r=.140 **p=.18**	r=.073 **p=.49**	r=.029 **p=.78**
Time spent after surgery	r=-.078 **p=.45**	r=-.273 ***p=0.009**	r=-.175 **p=.09**	r=.141 **p=.18**	r=.011 **p=.92**	r=. -239 ***p=0.022**	r=-.037 **p=.72**	r=.059 **p=.57**	r=.022 **p=.83**

BMI: Body mass index, **LE**: Life enhancement, **PP**: Physical performance, **PO**: Psychological outlook, **SI**: Social interaction, **PH**: Preventive health, **EM**: Exercise milieu, **TE**: Time expenditure, **PE**: Physical exertion, **FD**: Family discouragement**, NS:** Not significant, **r**: Spearman's rho, **p**<0.05, ***:** Significant at .05 level

word "while sitting". In our study, there was no significant relationship between the level of physical inactivity and perceived exercise beliefs and barriers except for age. Ottenbacher et al.[33] reported that change in perceived barriers was not associated with the change in physical activity among breast and prostate cancer survivors. Hsu et al.[17] also reported no significant relationship between exercise frequency and sociodemographic and clinical parameters among BC survivors. This insignificant relationship may be noteworthy to highlight that the perceived exercise beliefs and barriers are not directly linked to the level of physical activity. Yet, it might also be expectable to assume that higher perceived beliefs can lead to regular physical activity. Conversely, Gho et al.[19] reported being sufficiently or insufficiently physically active was found significantly correlated with the majority of domains of perceived exercise benefits and barriers. However, 61% of their sample was defined as "physically inactive". Nonetheless, age was found significantly correlated with the "Exercise Milieu" subscale of EBBS in which issues associated with reaching and performing exercise instead of the side effects of treatment are generally focused. This finding is important since the unmet rate of physical activity recommendations can originate from these perceived exercise barriers among older BCS. Our findings were also in parallel with the literature findings.[34,35] Hsu et al.[17] reported that the effect of social support was higher in the older age group compared to the younger ones. Similarly, Perry et al.[7] reported that the "lack of convenient exercise facilities" which is in parallel with the items of the EM subscale, was the main barrier to exercise among their patient cohort in which the mean age was above 70.

When it comes to the major perceived exercise barriers, treatment, and patient-related issues such as fatigue and feeling weak have been reported as the most remarkable ones.[16] Those are also understandable due to the side effects of the systemic therapy of cancer can last quite long even after years of the completion of primary treatment is a well-known point. Yet, lack of time and self-discipline, procrastination, and other factors such as enjoyment have also been reported as significant non-disease-specific barriers regarding exercise. In this manner, those barriers are also highlighted to be investigated in order to improve exercise and physical activity habits among the cancer population.[36] Due to the research design of our study, we did not investigate any theme or specific issue as barriers or beliefs. However, the "Physical Exertion" subscale, which is focused on tiredness and fatigue with a total of three items, was found relatively lower compared to the other subscales of perceived barriers in our study. When considering the perceived exercise beliefs, the "Life enhancement" subscale was higher by proportioning the mean score to the maximum score compared to the others. Our findings are compatible with the literature.[7,16] These findings can also be attributable to the time spent after surgery since the great majority of our sample had relatively below three years of the period after primary treatment. In addition, nearly half of our sample had a positive history of tamoxifen or aromatase inhibitor use, which has well-known side effects such as myalgia and arthralgia.[37]

The chronicity of survivorship of BC may affect participation in exercise or regular physical activity. Hsu et al.[17] reported that exercise frequency gradually decreased over time among BCS. In our study, we found weak but significant negative correlations among TSS, the "Physical performance" subscale of perceived exercise beliefs, and the "Exercise Milieu" subscale of perceived exercise barriers, respectively. Although the correlation levels were weak, these findings deserve to be noted that BCS may think that the benefits of exercise would steadily lose their importance after the completion of primary treatment according to the perceived exercise beliefs. These findings need to be addressed in detail since Charlier et al.[6] reported that the desired physical activity level was already below in BC patients who were in the six months of the completion of their treatment. In addition, the TSS might have played an important role in perceived exercise barriers according to the significant relationship between EM and time spent after surgery. We think that this was a remarkable result since the participation level of physical activity during the chronic stage of survivorship might dramatically be affected by other factors such as procrastination and/or lack of time instead of treatment-related side effects. Ottenbacher et al.[33] reported that "being busy" and "no willpower" as significant major perceived barriers among breast and prostate cancer survivors. Since it is well known that insufficient patient education is a major contributor to the perceived exercise beliefs and barriers,[16] informing patients about the benefits of exercise in early settings carries a great opportunity to preserve the desired levels of physical activity among BCS. Rogers et al.[38] recently reported a significant improvement was achieved and preserved in the early physical activity intervention group compared to the usual care group at the 12th month. The importance of timing was also highlighted in the recently published systematic review in which the effect of the intervention of physical activity remained efficacious after several months yet its effect diminished over time.[39] It was also reported that a "lack of information" about exercise acted as a significant barrier among cancer survivors.[7,16,40] Nevertheless, it was stated that BCS wish to have exercise counseling in their routine cancer care.[7]Gjerset et al.[41] reported that 76% of patients from their sample with different kinds of cancer were interested in receiving exercise counseling during their treatment. On the other hand, Gho et al.[42] reported that "bra discomfort" was one of the perceived barriers among BCS irrespective of age and/or other parameters. Therefore, filling the gap in information about the exercise should also include clothing and/or other discomforts that may impede participation in regular physical activity or exercise.

This study has some strengths and limitations. Using a validated questionnaire, a homogenous sample of cancer types, and filling out a questionnaire in a real environment instead of an online survey may present the strengths of this study. Nevertheless, a cross-sectional nature of study design and recall bias, especially evaluating total sitting time which can be over or under-reported as stated in the literature,[43]may have limited the revealing of potential associations and/or effects on exercise beliefs and benefits. In addition, we might have failed to investigate the total sitting time by using only a

question which is quite vulnerable to being scored biased. For instance, Lee et al.[30] reported that IPAQ-SF typically overestimates physical activity by nearly 85%. In addition, nearly all our patients were white Caucasian women, and included from a single oncology setting might hinder results from being generalizable to all BC survivors. Besides, assessing anxiety and depression would have improved the interpretation of our findings in the context of implications for clinical practice. Further studies should consider these issues when addressing and evaluating the specific needs and barriers to exercise among BCS.

CONCLUSION

Since the importance of physical activity is well understood among cancer patients, establishing sustainable, regular physical activity and exercise habits carries great importance. In this manner, addressing the specific needs, preferences as well as perceived beliefs and barriers upon exercise should be well documented to create a sustainable, long-lasting physical activity behavior among cancer populations. The findings of this study highlight the need for special attention to perceived barriers to exercise at higher ages. In addition, it might also be plausible to conclude that actions should be taken to prevent physical inactivity as much as earlier in the trajectory of breast cancer treatment according to the significant associations between time spent after surgery and perceived exercise beliefs and barriers.

Ethics Committee Approval: Ethical board approval was granted by the Ethics Committee of the University of Health Sciences with the protocol number 11092019/02.

Informed Consent: All participants were informed before the enrollment of this study and written informed consent was taken

Author Contributions: Concept-AT, YB, MA; Design-AT, YB; Supervision-AT, MA; Resources-AT, MA; Materials-AT, YB, MA; Data Collection and/or Processing-AT, MA; Analysis and/or Interpretation- AT, YB; Literature Search- AT; Writing Manuscript- AT, YB, MA;; Critical Review- AT, YB

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PHYSIOLOGICAL EFFECTS OF IMPACTED MESIODENS ON THE DEVELOPMENT OF ADJACENT TEETH
GÖMÜLÜ MEZİODENSLERİN KOMŞU DİŞLERİN GELİŞİMİ ÜZERİNDEKİ FİZYOLOJİK ETKİLERİ

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ABSTRACT

In the present retrospective study, it was aimed to analyze the physiological effects of impacted mesiodens on adjacent teeth with dental and chronological age determination in cone beam computed tomography (CBCT). In the study, 68 CBCT images were examined. Two groups were formed, including 34 individuals with mesiodens (mesiodens group) and 34 without mesiodens (control group). Dental age and chronological age were compared in both groups. Demirjian's method was utilized to determine the dental age. The position and location of mesiodens were categorized. Statistical analysis was performed with SPSS software version 18.0 (Chicago, IL, USA). Median diastema was seen in 16 cases (47.10%) in the mesiodens group. The mesiodens was most commonly impacted in the palatal (76.50%, n=26) and vertical (n= 19, 55.90%) position. There were significant differences between the incisor tooth development scores of the groups (p= 0.047 and p= 0.030, respectively). While the prevalence of H score of bilateral incisors in the control group (88.20% for both incisors) was higher than that of the mesiodens group (58.20% for both incisors), the G score was higher in the mesiodens group (20.60% and 23.50%) than in the control group (2.90% for both teeth). Mesiodens can delay root development of adjacent teeth. For this reason, extraction of these teeth may be considered in the early period to avoid affecting adjacent teeth and anatomical structures. It may also cause erroneous calculations in dental age determination. This situation should be taken into account in terms of forensic dentistry.

Keywords: CBCT, demirjian, dental age estimation, mesiodens.

ÖZ

Bu retrospektif çalışmada, Konik Işınlı Bilgisayarlı Tomografide (KIBT) gömülü meziodenslerin komşu dişler üzerindeki fizyolojik etkilerinin dental ve kronolojik yaş tayini ile analiz edilmesi amaçlanmıştır. Çalışmada 68 KIBT görüntüsü incelendi. 34 meziodensi olan (meziodens grubu) ve 34 meziodensi olmayan birey (kontrol grubu) olmak üzere iki grup oluşturuldu. Diş yaşı ve kronolojik yaş her iki grupta karşılaştırıldı. Diş yaşını belirlemek için Demirjian yöntemi kullanıldı. Meziodenslerin pozisyonu ve konumu kategorize edildi. İstatistiksel analiz SPSS yazılımı sürüm 18.0 (Chicago, IL, ABD) ile yapıldı. Meziodens grubunda 16 (%47.10) olguda orta hatta diastema görüldü. Meziodens en sık palatinal konumda (%76.50, n=26) ve vertikal (n= 19, % 55.90) pozisyonda görüldü. Grupların kesici diş gelişim skorları arasında anlamlı fark vardı (sırasıyla p= 0.047 ve p= 0.030). Kontrol grubunda bilateral kesici dişlerin H skoru prevelansı (her iki kesici diş için %88.20) meziodens grubundan (her iki kesici diş için %58.20) daha yüksek iken, G skoru meziodens grubunda kontrol grubuna göre (%20.60 ve %23.50) daha yüksekti (Her iki diş için %2.90). Meziodens komşu dişlerin kök gelişimini geciktirebilir. Bu nedenle komşu dişlerin ve anatomik yapıların etkilenmemesi için erken dönemde bu dişlerin çekimi düşünülebilir. Diş yaşı tespitinde de hatalı hesaplamalara neden olabilir. Bu durum adli diş hekimliği açısından dikkate alınmalıdır.

Anahtar kelimeler: KIBT, demirjian, diş yaşı tayini, meziodens

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INTRODUCTION

Dental anomalies may appear as anomalies of shape, number, or size of teeth in general. Supernumerary teeth, one of the number anomalies, can be seen in both permanent and primary dentition. Although supernumerary teeth are not common formations, their incidence in the clinic may vary depending on many factors.[1] Considering the gender variable, the incidence of supernumerary teeth is higher in men than in women.[2,3] However, supernumerary teeth can be found in many quadrants of the jaws. It often accompanies the clinical findings of Down syndrome, Ellis-Van Creveld syndrome and Ehler Danlos syndrome.[4] They are seen between the central incisors and are specifically called mesiodens.

Mesiodens are the most common supernumerary teeth with a prevalence of 0.15-1.90% in the general population.[5] These teeth can be impacted or inverted.[1] Mesiodens are classified into two subgroups according to their shape and size. The first group includes mesiodenses of normal shape and size, while the second group includes mesiodenses of amorphous shape and size.[4] Although there are many theories about the etiology of mesiodens, there is no definite information about their formation. The most accepted view is that the lingual extensions of the dental bud, which is formed due to increased activity in the dental lamina cause mesiodens formation.[6,7] Only 25% of the mesiodens appear in the mouth. These teeth, which are more in the maxilla anterior, affect growth and development more than those in the posterior region and cause aesthetic-functional complications. Some of the complications caused by mesiodenses are eruption problems in permanent teeth, root malformations, crowding and diastema in anterior teeth.[8] Studies have shown that mesiodenses in vertical positions cause more delays in tooth eruption than in inverse positions.[9,10]

Age determination is a necessary examination in forensic dentistry, anthropology, forensic medicine, pediatrics, and orthopedics. It is important for the treatment planning of living individuals as well as forensic cases. Odontological data are important in forensic studies related to age determination. Teeth are frequently used in age determination as they are the hardest structures of the body, least damaged by external factors, and least affected by nutrition and systemic diseases. Dental age estimation by radiographic methods is non-invasive and take relatively less time compared to other methods.[11-13]

Mesiodens can be detected on any plain tooth radiograph that includes the premaxillary region. However, in two-dimensional radiographs, the superposition of mesiodens on adjacent structures may cause misinterpretation due to its disadvantages such as magnification and loss of clarity. Therefore, it is important to determine the three-dimensional (3D) location of the mesiodens in order to reach a definitive diagnosis and treatment plan. CBCT is preferred in maxillofacial imaging due to its advantages such as fast scanning time, image accuracy and reduced patient radiation dose compared to other three-dimensional imaging methods.[14]

The basis of radiological methods in dental age determination is based on determining the developmental stage of the teeth with the help of radiographs and determiningthe tooth age by comparing the data with the tooth development scales formulated by different researchers.[15] Among these researchers , the most used method of calculating tooth age is the method developed by Arto Demirjian.[16]

The developmental stages of 7 teeth in the mandible are evaluated in calculating tooth age with the Demirjian method.[17] This method has also been tested on people living in different regions and positive results have been obtained.[18-21]

In this study, we hypothesized that the presence of mesiodens does affect the development of adjacent maxillary central teeth.

The aim of this study is to precisely define the 3D position of the mesiodens using CBCT and examine its effects on the root development of adjacent teeth.

MATERIALS AND METHODS

The study protocol was carried out according to the principles described in the Declaration of Helsinki, including all changes and revisions. The Local Ethics Committee of Bolu Abant İzzet Baysal University was approved the study (protocol no:2021/144).

The images of the patients who had CBCT between 2018 and 2021 years in the Dento-maxillofacial Radiology Clinic were scanned retrospectively. The CBCT scans were obtained using an I-Cat imaging system(17-19 Model, Imaging Sciences International, Hatfield, PA, USA) at 120 kVp and 15 mA, with a voxel size of 0.3 mm and an exposure time of 4.8 sec. Images were investigated using i-CAT vision Q imaging software. Dental arches in the upper alveolar process from the lower edge of the nasal cavity and the anterior region of the maxilla were included in the field of view (FOV) of all individuals with CBCT. CBCT examinations were performed by an oral and maxillofacial radiologist and surgeon with three years of experience.

Patients with pathological conditions such as trauma, presence of congenital malformed incisors, mesiodens teeth erupted into the mouth, presence of plate and screw, bone graft material, cyst, tumor, and anterior maxilla fracture were not included in the study. Also, the presence of artefacts in the anterior maxilla were excluded from the study. Patients aged between 7 and 25 years with embedded mesiodens in the anterior maxilla were included in the study. In the radiographs examined, they were examined as multi-plane images with a thickness of 0.3 mm and the presence and position of mesiodens in all sections (coronal, sagittal, vertical planes) were evaluated (Figure 1).

Two groups were formed, including 34 individuals with mesiodens (mesiodens group) and 34 without mesiodens (control group). If there is a mesiodens, its position were stated and root development stage were evaluated according to the Demirjian method [16](Figure 2).

Additionally, the age and gender of the patients were recorded. If there was disagreement between two observers and consensus could not be reached, a third observer was consulted to reach agreement. To analyze intraobserver agreement, 8 randomly selected cases were evaluated and repeated one week later.

Statistical Analysis

A priori power analysis was performed based on the repeated Kappa Test using the software G*power version 3.1.9.4.[22] A sample size of 68 was found to be ade-

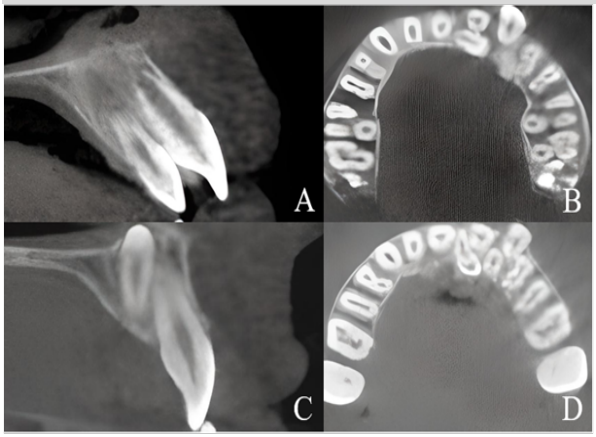

Figure 1.The orientation of unerupted supernumerary teeth is classified into 4 directions such as vertical **(A),** horizontal **(B)**,

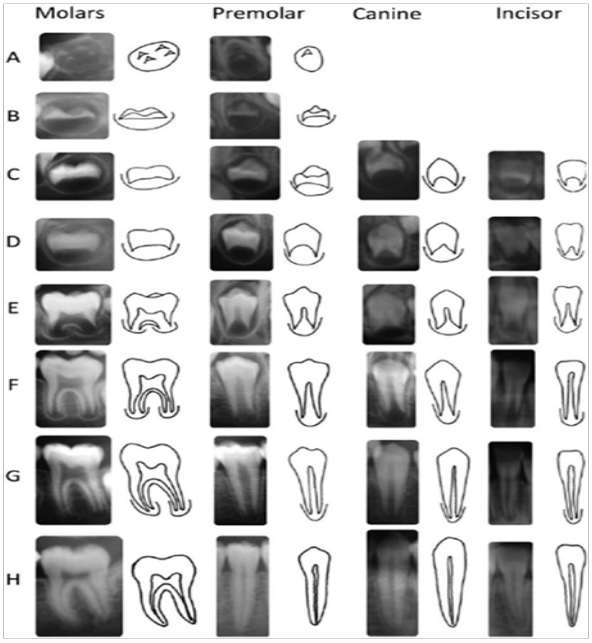

Figure 2. Developmental stages in Demirjian's method[16]

quate to detect a difference in terms of the effect size of f=0.25 with 80% statistical power at α = 0.05. Study data was analyzed using SPSS software version 18.0 (Chicago, IL, USA). Intraobserver reliability was examined by Kappa Test. The level of interobserver agreement and the intraobserver reliability of both observers were excellent. The compatibility of the ages of the individuals included in the study with the normal distribution was made with the Shapiro-Wilks test, and the comparison of the mean ages between the two groups according to the tooth stages was made with the independent sample t-test. Age differences between within-group tooth stages were analyzed with the one-way ANOVA model, and the stages that were significantly different were analyzed with the Tukey post-hoc test. The distribution of tooth development stages was analyzed with the chi-square test. $p<0.05$ was accepted as statistical significance level.

RESULTS

The study sample included 34 patients with mesiodens (35% females, 65 % males; age range: 7–25 years; mean age**:** 14.05 ± 5.39) and 34 controls (41% females and 59% males; mean age: 14.14±5.47). In both groups, no statistically significant difference was observed according to age and sex (p= 0.945 and p=0.803, respectively).

Median diastema caused by mesiodens was seen in 16 cases(47.10%). In bucco-palatal direction, mesiodens were most frequently observed in the palatal position (76.50% , n=26).

According to the results of direction of impaction, mesiodenses were most frequently observed in the vertical position (n= 19, 55.90%). Horizontal position was very rarely observed (14.70%) appearing in only 5 cases, and inverted orientation were seen in 10 cases (29.40%) (Table 1).

There was no significant relationship between the presence of diastema and the bucco-palatal position of the mesiodens (p= 0.429) and the direction of impaction (p= 0.500).

In addition, there was no significant difference between the adjacent incisive teeth development scores and bucco-palatal positions and the direction of impaction of the mesiodens (p= 0.841 and p= 0.929, for right central incisor, respectively; p= 0.718 and p= 0.885, for left central incisor, respectively).

Table 2 shows tooth formation of right and left central incisive teeth of each group. A significant difference was found between incisive teeth development scores by groups (p=0.047and p=0.030, respectively).

While the root maturation completion rate of bilateral incisors in the control group was high with an H score

Table 1. Demographic and radiographic characteristics of cases.

Variables		Mesiodens n (%)	Control n (%)
Gender	*Male*	22 (64.7)	20 (58.8)
	Female	12 (35.3)	14 (41.2)
Age	*mean±SD**	14.05±5.39*	14.14±5.47*
Bucco-palatalposition	*Palatalposition*	26 (76.5)	-
	BuccalPosition	8 (23.5)	-
Direction of impaction	*Vertical*	19 (55.9)	-
	Horizontal	5 (14.7)	-
	Inverted	10 (29.4)	-
Mediandiastema	*Present*	16 (47.1)	-
	Absent	18 (52.9)	-

SD: Standard Deviation.
**Numerical data*

Table 2. Distribution and comparison of maturation levels of centralincisors according to groups

	Right Central Incisor		Left Central Incisor	
	Mesiodens (n=34)	**Control (n=34)**	**Mesiodens (n=34)**	**Control (n=34)**
D	1 (2.9%)	0	0	0
E	3 (8.8%)	2 (5.9%)	5 (14.7%)	3 (8.8%)
F	3 (8.8%)	1 (2.9%)	1 (2.9%)	0
G	7[a] (20.6%)	1[b] (2.9%)	8[a] (23.5%)	1[b] (2.9%)
H	20[a] (58.8%)	30[b] (88.2%)	20[a] (58.8%)	30[b] (88.2%)
p	0.047*		0.030*	

*Differentupper letters show significant difference between columns. *Statistically significance level is at p<0.05.*

(88.20%), the root maturation was more in the G score (20.60% and 23.50%) in the mesiodens group. D score was determined only in one case belonging to the mesiodens group (Figure 3).

Table 3 shows the distribution of development scores of all teeth by groups. It was determined that root maturation increased with increasing age in the mesiodens groups (p= 0.001 for the right central, p= 0.005 for the left central).

The majority of cases in the control group had an H score. No statistically significant difference was observed in terms of mean age between the groups in each scoring (p>0.05).

DISCUSSION

Supernumerary teeth are a number anomaly. They are frequently encountered in the anterior region of the maxilla.[3] Supernumerary teeth seen between the inci-

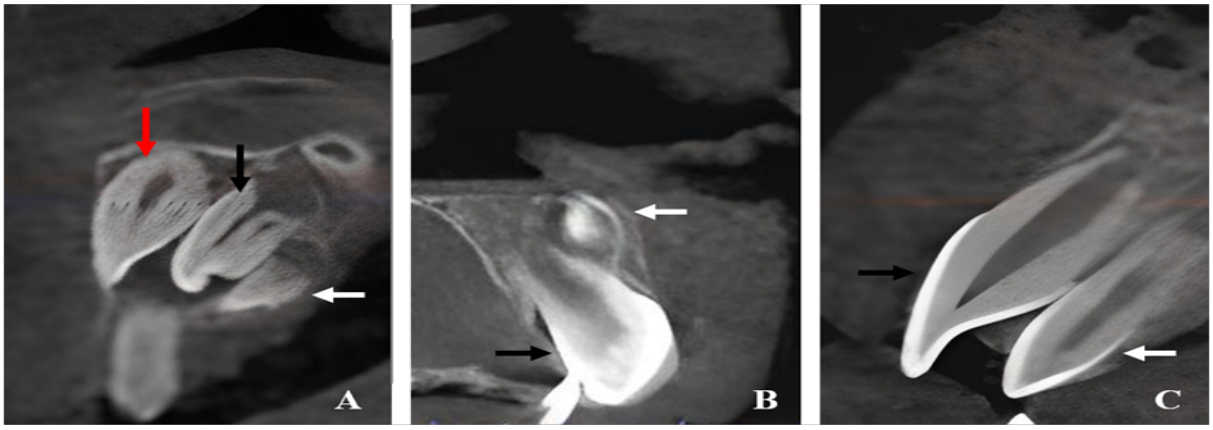

Figure 3. A. CBCT image of the patient with a D score. Red arrow: Upper lateral incisor tooth, Black arrow: Upper santral incisor tooth, White arrow: Mesiodens. **B.** CBCT image of patient with an E score; Black arrow: Upper santral incisor tooth, White arrow: Mesiodens, **C.** CBCT image of patient with a G score, Black arrow: Upper santral incisor tooth, White arrow: Mesiodens.

Table 3. Comparison of ages according to dental maturation level score (E-H).

Teeth	*Groups*	E	F	G	H	p
Right Central incisor	***Mesiodens***	8.250 ±0.957[a]	9.333 ±.577[b]	10.857 ± 1.864[c]	17.210 ± 5.137[d]	0.001
	Control	7.000±0.000	8	9	15.000±5.258	
	P	*0.157*	-	-	*0.155*	
Left Central incisor	***Mesiodens***	9.400±2.701[a]	-	10.875±1.356[b]	16.650 ±5.556[c]	0.005
	Control	7.333±0.577[a]	-	9	15.000 ± 5.525[b]	
	P	*0.252*	-	-	*0.293*	

*Statistically significance level is at p< 0.05.
*No comparison was made for D level due to the being present in just one teeth.
*Different upper letters show significant difference between columns (The comparison of the meanage of the scores with the ANOVA test for the mesiodens group, p=0.001 for the right central, p=0.005 for the left central). *Since the majority of the patients in the control group had an H score, the ages of the scores did not be compared.
*P values in the rows belong to the independent samples t-test, which the meanages of the control group and mesiodense group are compared according scores.
*Since there was one case each in certain groups in the G and F scores, the average ages of the mesiodense and control groups could not be compared. Descriptive values for the age of each case are given in the table.

sors are called mesiodens. Mesiodens may cause delay in the eruption of permanent teeth, midline diastema formation, tooth displacement and cyst formation.[23,24] It is reported in the literature that it causes root resorption and cyst formation in permanent teeth.[25,26] In this study, median diastema was observed in 47.10% of mesiodens cases, while root resorption and cyst formation were not observed in the examined cases.

Tay et al.[23] found in their study that the incidence of mesiodens was 84.30% in men and 15.60% in women. Thomas van Arx et al.[27] found mesiodens at a rate of 72.20% in men and 27.70% in women, supporting these data in their study. Kim et al.[28] found that the prevelance of mesiodens in children was 71.70% in males and 28.30% in females. Barham et al.[14], Mason et al.[29], and Kocataş et al.[30] also found the male-female ratio as 2.4:1, 2:1 and 3:1, respectively, in their studies on excess teeth in the jaws. In the presented study, the finding that the incidence of mesiodens is higher in men supports these data (64.70% male, 35.30% female).

In a study of 90 patients, Thomas van Arx et al. [27] found that 78% of the patients had a only one mesiodens tooth, 20% had two mesiodens teeth, and 2% had multiple mesiodens teeth. In this study, all except that twopatients had only one mesiodens.

Smailiene et al. [31] and Liu et al. [32] found in their radiological examinations on mesiodens teeth that these teeth are often located in the palatal position. In the present study, mesiodens buried palatinally was observed in 26 cases, while it remained buried in the buccal area in 8 patients.

In studies on mesiodens, researchers also evaluated the burial aspect of the mesiodens. Thomas van Arx et al.[27] found in their study on 90 patients that 44% of the cases were in the vertical position. They found mesiodens in the inverse position in 37% of the patients. Kocataş et al.[30] found in the data collected from 34 patients that the mesiodenses were vertical in 31 patients, inverse in 2 patients, and horizontal in 1 patient. Rajab et al.[33] found mesiodens in the vertical position at a rate of 83.10% in their study. 10.10% of the cases consisted of mesiodens in the inverse position. Gregg et al. [9] similarly showed that 67% of the supernumerary teeth, which cause delayed eruption in permanent teeth, are in the vertical position. In this study, similar to these researchers, mesiodens teeth were found in vertical position in 19 cases, inverse position in 10 cases, and horizontal position in 5 cases. However Liu et al. [32], Kim et al.[28] and Tay et al. [23] found most of the mesiodens in the inverse position in their studies. This difference may be due to the different populations studied.

Yun-Hoa Jung et al.[34] found that the presence of teeth in an inverted position was 60.60% and that teeth in a vertical position caused a greater delay in the eruption of adjacent teeth. Barham et al.[14] observed that 6.30% of individuals with mesiodens had a delay in the eruption of the adjacent tooth. They also reported that root development was incomplete in 71.60% of the teeth adjacent to the mesiodens. In this study, the majority of the mesiodens were seen in a vertical position, but the relationship between the position of the mesiodens and the adjacent tooth development stages was found to be statistically insignificant.

In some studies, it is stated that mesiodens causes a delay in the formation of adjacent tooth roots. It has also been observed that these teeth do not erupt into the mouth.[35,36] Mallineni et al., calculated a lower dental age in patients with supernumerary teeth, but the results were not statistically significant. They observed a greater delay in dental age in male patients with bilateral supernumerary teeth.[37] In this study, when the average ages of the teeth were compared with each score, no significant difference was found between the mesiodens and contol groups. However, when looking at the distribution of the scores of the right and left central teeth, the G score was higher in the mesiodens group than in the control group, and the prevalence of H scores was higher in the control group. This situation can be interpreted as the mesiodens may prolong the transition time from the G phase to the H phase in some cases.

The main limitation of this study is that the voxel size of the images is 0.3 mm. In high resolution images obtained with smaller voxels, the 3 dimensional position of the mesiodens and the developmental stages of the affected teeth can be observed more clearly and more accurate results can be obtained. Another limitation of the study is the small sample size due to age restrictions.

CONCLUSION

Mesiodens are the supernumerer teeth with a rate of 0.15- 1.90%. The higher prevalence of G score in the mesiodens group and H score in the control group in the present study suggests that mesiodens may prolong the transition time from G phase to H phase. These teeth can delay the root tip formation of adjacent teeth. It may cause miscalculations in the determination of dental age. This situation should be considered for the forensic dentistry. Also, in the presence of mesiodenses the development of adjacent teeth can be evaluated with CBCT, and early extraction of supernumerary teeth can be considered so that it does not affect tooth development. The most important limitation of this study is the small sample size. More precise results can be obtained with studies to be carried out with larger samples in larger archives.

Ethics Committee Approval: Ethics committee approval was received for this study from the Review Committee of the Bolu Abant İzzet Baysal University (protocol no:2021/144).

Informed Consent: Due to the retrospective design of the study, participant consent was obtained only for CBCT imaging.

Peer-review: Externally peer-reviewed.

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THE GENOMIC LANDSCAPE OF THE SWITCH/SUCROSE NON-FERMENTABLE CHROMATIN REMODELING COMPLEX IN ACUTE MYLEOID LEUKEMIA
AKUT MİYELOİD LÖSEMİDE SWITCH/SUKROZ FERMENTE EDILEMEZ KROMATİN YENİDEN ŞEKİLLENDİRME KOMPLEKSİNİN GENOMİK GÖRÜNÜMÜ

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ABSTRACT

The SWI/SNF chromatin remodeling complex is involved in the regulation of gene expression required for processes such as cell maintenance and differentiation in hematopoietic stem cells. Abnormalities in the SWI/SNF subunits involved in the homeostasis of hematologic processes contribute to the initiation or progression of hematologic malignancies, but the mechanisms underlying this phenotype are not yet fully understood. The aim of study is to comprehensively identify mutations and expression profiles in the genes forming the SWI/SNF complex using bioinformatics tools, with a focus on understanding the underlying mechanisms. Genomic sequences and expression profiles of an AML cohort (n:872) were obtained from using tools and subsequently analyzed. PolyPhen-2, SIFT, and Mutation Assessor tools were used to estimate the oncogenic/pathogenic effects of mutations identified in 9 genes encoding subunits of the complex *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A*in AML pathogenesis. STRING analysis was performed to better understand the functional relationships of the mutant proteins in cellular processes.Furthermore, to the mutation profile, gene expression and survival profiles were also determined. A total of 17 genetic abnormalities were determined in 9 genes, including 9 missense, 6 frameshift mutations, 1 mutation in the splice region, and 1 fusion mutation. In the AML cohort, the expression levels of *ARID1A, ARID1B, SMARCA2*, and *PMBR1*were significantly higher in the patient group compared to the healthy group ($p<0.01$). Survival analysis based on low and high gene expression profiles showed no significant difference in results. In STRING analysis, our genes were found to have functional relationships with the PHF10protein, which is involved in cell cycle control. The results suggest that the

ÖZ

SWI/SNF kromatin yeniden modelleme kompleksi, hematopoietik kök hücrelerde hücre bakımı ve farklılaşma gibi süreçler için gerekli olan gen ekspresyonunun düzenlenmesinde görev alır. Hematolojik süreçlerin homeostazında yer alan SWI/SNF kompleksi alt birimlerindeki değişiklikler hematolojik malignitelerin başlamasına veya ilerlemesine katkıda bulunmaktadır, ancak bu fenotipin arkasındaki mekanizmalar tam olarak açıklanmamıştır. Çalışmada, SWI/SNF kompleksini oluşturan genlerde mutasyonların ve ekspresyon profilinin biyoinformatik araçları kullanılarak kapsamlı belirlenmesi amaçlanmıştır. AML kohortuna (n:872) ait genom dizileri ve ifade profillerine biyoinformatik araçlar aracılığı ile elde edilmiş ve analiz edilmiştir. Kompleksin alt ünitelerini kodlayan 9 gende *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1* ve *BCL7A* belirlenen mutasyonların AML patogenezinde onkojenik/patojenik etkilerinin tahmini PolyPhen-2, SIFT ve Mutation Assessor araçları kullanılmıştır. Mutasyona uğrayan proteinlerinin fonksiyenel etkilerini anlamak içinSTRING aracı ile analiz gerçekleştirilmiştir. Mutasyon profili değil aynı zamanda mutasyon varlığının gen ifadesi ve sağ kalım üzerine etkileride değerlendirilmiştir. 9 gende 9 yanlış anlam, 6 çerçeve kayması mutasyon, 1 splize bölge ve 1 füzyon mutasyonu olmak üzere toplam 17 genetik anormallik belirlenmiştir.AML kohortunda *ARID1A, ARID1B, SMARCA2 ve PMBR1*ekspresyon seviyelerin hasta grubunda sağlıklı gruba yüksek ve istatistiksel olarak anlamlıdır ($p<0.01$). Düşük ve yüksek gen ekspresyon profillerine göre yapılan sağ kalım analizi sonuçlarımızda bir farklılık görülmemiştir. STRING analizinde, hedef genlerimizin, hücre döngüsü kontrolünde görev alan PHF10ile fonksiyonel ilişkileri bulunduğu belirlenmiştir. Sonuç olarak, sonuçlarımız, *ARID1A, ARID1B, SMARCA2, SMARCA4 ve PBRM1'de* tespit ettiğimiz mutasyonlarının, SWI/SNF kromatin yeniden modelleme komplekslerinin fonksi-

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mutations identified in the *ARID1A, ARID1B, SMARCA2, SMARCA4*, and *PBRM1*may disrupt the function of SWI/SNF chromatin remodeling complexes, possibly inducing/activating different cellular pathways involving different chromatin environments during AML pathogenesis.

Keywords: AML, chromatin remodeling,gene expression, mutation, SWI/SNF complex

yonunu bozarakAML patogenezi sırasında farklı kromatin ortamlarını içeren farklı hücresel yolları indükleyebileceği/inaktive edebileceğini düşündürmektedir.

Anahtar Kelimeler: AML, gen ifadesi, kromatin remodülasyonu, mutasyon, SWI/SNF kompleksi

INTRODUCTION

The The Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex is a group of protein complexes responsible for regulating the organization of proteins around the cell's genetic material. This complex modulates gene expression by altering the structure of chromatin, allowing access to the genetic information of cells in various processes. Functionally, it operates by histone modification and nucleosome sliding.[1,2] The complex complex alters the structure of chromatin by modifying histone proteins around Deoxyribonucleic Acid (DNA). These histone modifications can loosen or tighten the binding of histones to DNA, thereby affecting the accessibility and expression of genes. Alternatively, it changes the physical access to DNA by shifting structures called nucleosomes, where DNA and histone proteins come together. This can influence the opening or closing of gene promoter regions, thus controlling gene expression.[3-5] In cancer, the function of the SWI/SNF complex can be disrupted or mutated. This can often contribute to the dysregulation of critical cellular processes such as cell cycle control, cell differentiation, and apoptosis, thereby contributing to cancer development.[6] Cancer genome studies have found a high prevalence of mutations in genes encoding subunits of the SWI/SNF chromatin remodeling complexes, with approximately 20-25% of all cancers having abnormalities in one or more of these genes.[6-8] Overall, the mammalian SWI/SNF complex is an evolutionarily conserved chromatin remodeling complex composed of more than 20 subunits.The SWI/SNF chromatin remodeling complex consists of genes including ARID1A (AT-rich interaction domain 1A), ARID1B (AT-rich interaction domain 1B), SMARCA2 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 2), SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4), SMARCE1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1), SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1), DPF2 (Double PHD Fingers 2), PBRM1 (Polybromo 1), and BCL7A (B-cell CLL/lymphoma 7A).[4,7,10] SWI/SNF complexes are Adenosine Triphosphate (ATP)-dependent chromatin remodeling proteins capable of displacing, removing or altering the composition of nucleosomes by ATP hydrolysis. Due to this activity, the complexes play a crucial role in normal physiological activities in cells by ensuring the appropriate expression of genes in processes such as replication, transcription, translation and post-translational modifications.[6,8-10] Hematologic malignancies represent a very heterogeneous group of diseases with different molecular and phenotypic features. Adequate SWI/SNF function is crucial for various differentiation processes, including hematopoiesis and hematopoietic stem cell maintenance.[7,11-13]

In addition, genetic abnormalities in the subunits of the SWI/SNF complex, particularly *ARID1A/1B/2, SMARCA2/4*, and *BCL7A*, are common in various lymphoid and myeloid malignancies. Most genetic abnormalities in the complex lead to a loss of function of the subunit and the acquisition of oncogenic mechanisms, suggesting a tumour suppressive role of the genes forming the complex.[2,11-13] Although more than 20 % of tumors and hematological malignancies in children and adults are characterized by a deficiency of the SWI/SNF complex, the molecular background of this phenotype is not yet fully understood.[2,10,14,15] In particular, there is increasing evidence that mutations in the subunits of the SWI/SNF complex confer resistance to various antineoplastic agents used in the treatment of hematologic malignancies.[10,12,13,16,17] Studies that elucidate the function of SWI/SNF and the outcomes of SWI/SNF abnormalities in detail are often lacking, especially in hematologic malignancies. Therefore, we aimed to establish a comprehensive genetic profile to understand the contribution of mutations or inactivation of genes encoding the subunits of the SWI/SNF complex to the pathogenesis of Acute Myeloid Leukemia (AML).

MATERIAL AND METHODS

Design of the Study Group

The AML (n:872) data set was downloaded from the cBioPortal database and the study's raw data accessible via cBioPortal. Data were downloaded on September 02, 2023.

Mutation Profile Analysis

The CBio Cancer Genomics Portal (http://cbioportal.org) is a freely accessible tool that provides mutation data from The Cancer Genome Atlas (TCGA) as a data source.[18] The AML was selected as the cancer of interest to comprehensively investigate mutations in the *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A* in AML samples (n:872) via the web interface. Comprehensive mutation profile analyzes were then performed using the functions provided by the interface for the genes of interest, using the tools provided by the Cbio portal.

Functional/Pathogenic Effect Analysis of Identified Mutations

Scores provided by the Polymorphism Phenotyping v2 (PolyPhen-2), Sorting Intolerant from Tolerant (SIFT), and Mutation Assesor databases were used to identify the potential pathogenicity and clinical impact of muta-

tions identified in the *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2*, *PMBR1* and *BCL7A*. PolyPhen-2 is an online accessible tool that estimates the potential impact of mutations on protein stability and function by using structural and comparative evolutionary analyzes of amino acid positions for potential mutations and Single Nucleotide Polymorphisms (SNPs).[19] PolyPhen-2 assesses the likelihood that a missense mutation will cause damage to the protein based on a combination of these properties, gives the user a score, and categorizes the result as likely deleterious, possibly deleterious, benign, and unknown. The SIFT (https://sift.bii.a-star.edu.sg/) is a tool that estimates whether a change in amino acid position can impact protein function based on sequence homology and the physical properties of amino acids.[20] SIFT separates an amino acid substitution as either bearable or detrimental to protein function. Mutation Assessor (http://mutationassessor.org/r3/) estimates the functional effects of amino acid substitutions in proteins, including mutations found in cancer or polymorphisms. The assessment is based on the evolutionary preservation of the impacted amino acid in protein homologs.[21]

Identification of Differentially Expressed Genes and Survival Analysis

GEPIA (Gene Expression Profiling Interactive Analysis) (http://gepia.cancer-pku.cn/) is a database that allows users to perform differential expression analysis at the subtype level.[22] GEPIA is used to analyze the expression of genes and isoforms by comparing TCGA data. Therefore, we used this data provider to determine the differential expression of the *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A* in AML cohorts (n:173) and healthy tissue samples. Boxplots were generated using Ribonucleic acid–sequencing (RNA-Seq) normalized expression levels, and statistical tests were automatically calculated by the GEPIA. p-values were automatically calculated, and p-values below 0.05 were considered statistically significant.TPM (Transcripts Per Million) were used to measure m-Ribonucleic Acid (RNA)expression levels. The expression data are first log2 (TPM+1) transformed for differential analysis and the log2FC is determined as median (Tumor)-median (Normal). Genes with higher [log2FC] values and lower q values than pre-set thresholds are considered differentially expressed genes.

Protein- Protein Interaction Analysis

The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org) is used to determine protein-protein interactions.[23] The purpose of this database is to create a comprehensive and objective global network that includes both physical and functional interactions. The predicted interactions of ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1, and BCL7A proteins were determined by STRING, which identifies physical and functional relations between proteins.

Statistical Analysis

All statistical analyzes used in the analysis of the study data were performed using the GEPIA database. The GEPIA database uses the differential analysis method to compare gene expression in tumor and healthy study groups. The test used to calculate differential expression is the one-way Analysis of Variance (ANOVA). The analysis of overall survival was performed using Kaplan-Meier curves, with the log-rank test used to compare low and high expression groups. For all tests performed, a statistically significant value was considered to be $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics of the Study Group

Detailed demographic and clinical characteristics of the dataset consisting of 872 AML patients are presented in Table 1.

Results of Mutation Profile in SWI/SNF Complex Genes in AML

In the AML cohort (n:872), mutations in the study genes were identified in 2.5% of patients, with the highest mutation frequency observed in the *ARID1A* (0.8%), while no mutations were detected in the *SMARCE1*. A total of 17 mutations were identified in 9 genes, including 9 missense, 6 frame shift and 1 splice domain mutation. Table 2 contains detailed information on the identified mutations. Figure 1-A shows the frequency of mutations in the genes of the AML cohort, and Figure 2 illustrates the localization of mutations in the domains of the proteins. The somatic mutation frequency of the *ARID1A* was detected to be 0.7%, with two of the identified mutations being putative driver mutations. The driver mutations p.S446Lfs176 and p.S949Hfs57 could lead to a shift in the reading frame, possibly resulting in premature termination of the polypeptide and the formation of a truncated protein. The p.G1234D missense mutation is located in the HIC1 binding domain, while the p.R1658Q mutation is located in the GR binding domain. The ARID1A-RPS6KA1 fusion was identified as a structural variant. Three frame-shift deletions altering the reading frame and a p.R2128P missense mutation in the DUF3518 domain were detected in *ARID1B*. The somatic mutation frequency of the *ARID1B* was detected to be 0.5%.In *SMARCA2*, the p.X119_splice mutation was found at the boundary between exon 13 and intron 14, i.e. in a splice site that is 100% conserved across all species. In addition, the p.V685L and p.L753F missense mutations on *SMARCA2* are located in the helicase ATPase binding domain. The somatic mutation frequency of the *SMARCA2* was 0.3%.The p.P653Rfs*121 frameshift mutation in the BRK domain of *SMARCA4* is a driver mutation that could lead to premature termination of the polypeptide and the formation of a truncated protein. The somatic mutation frequency of the *SMARCA4* was 0.1%. Gene amplification abnormalities were also observed in *SMARCA2*, *SMARCA4* and *SMARCB1.DPH2* had two missense mutations, p.C295S and p.G302R, in the PHD finger domain, which serves as a bridge for the components of the SWI/SNF complex. The somatic mutation frequency of the *DPH2* was 0.2%.The somatic mutation frequency of the *PBRM1* was 0.3%, with the p.K250R missense mutation identified in the Br domain and the P919Q mutation in the BAH domain.

In Silico Pathogenic/Oncogenic Feature Analysis of Identified Mutations

The PolyPhen-2, SIFT, and Mutation Assessor were used for in silico analysis to predict pathogenic/oncogenic traits. According to the analysis results of these three

programs, 5 of the 17 mutations identified in our study were classified as disease-causing. Detailed information on the mutations with oncogenic/pathogenic character can be found in Table 1. In addition, the Onco KB database classified the mutations p.S446Lfs176, p.S949Hfs57 in *ARID1A*, ARID1A-RPS6KA1 fusion mutations, *SMARCA2* p.X119_splice and *SMARCA4* p.P653Rfs*121 as oncogenic.

Survival Analysis and Expression Profile of Key Genes

The gene expression profiles of *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1* and *BCL7A* were analyzed using the AML cohort (n:173) and the matching healthy tissue (n:50) available on GEPIA. The expression levels of *ARID1A, ARID1B, SMARCA2,* and *PMBR1* were upregulated in the patients

Table 1. Demographic, clinical and genetic data of patients with AML

	Patient data n: 872(%)
Gender	
Male/Female/NA	311/251/200
Diagnosis age, years	(1-87)
Chromosomal abnormality	
t(8;21)	11 (1.2)
inv(16)	18 (2.0)
11q23	4 (0.4)
t(15,17)	15 (1.7)
Cytogenetic risk	
Favorable	109 (12.5)
Intermediate	116 (13.3)
Unfavorable	132 (15.1)
NA/other	214 (24.5)
Diagnosis type	
FAB subtype	
M0	10 (1.1)
M1	15 (1.7)
M2	13 (1.5)
M3	11(1.3)
M4	35 (4.0)
M5	32 (3.7)
M7	2(0.7)
NA/other	731 (83.8)
Overall Survival Status	
Living	282 (37.0)
Deceased	423 (55.5)
NA	57 (7.5)
Total Mutation Frequency in AML	**Case (Frequency%)**
ARID1A genetic alteration	0.8
ARID1B genetic alteration	0.5
SMARCA2 genetic alteration	**Characteristic** 0.5
SMARCA4 genetic alteration	0.3
SMARCE1 genetic alteration	0
SMARCB1 genetic alteration	0.1
DPF2 genetic alteration	0.3
PBRM1 genetic alteration	0.4
BCL7A genetic alteration	0

Abbreviations: NA: Not Applicable; M: Metastasis

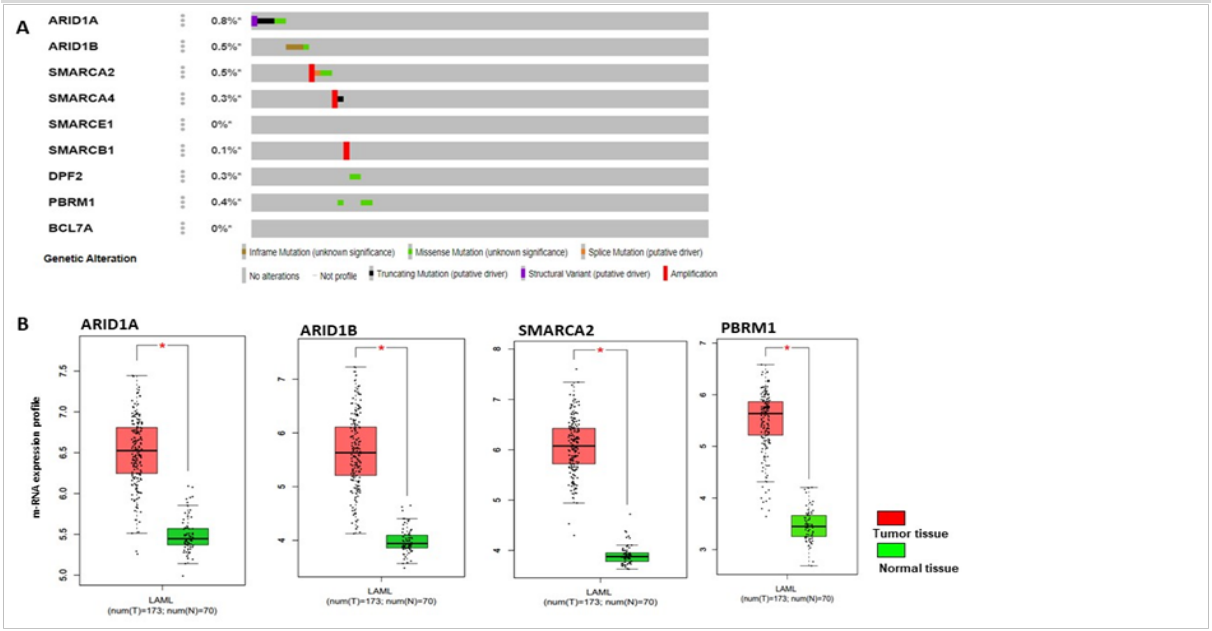

Figure 1: (A) Distribution of mutations in *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PBRM1*, and *BCL7A*genes in TCGA AML cohort from cBioPortal.Percentages of total mutations for each gene are given on the left**. (B)** GEPIA was performed to validate higher expression of thress hub genes (*ARID1A, ARID1B*, and *SMARCA2*) in AML samples compared with healthy samples. The red and green boxes represent AML and healthy tissues respectively. *represented p<0.01.

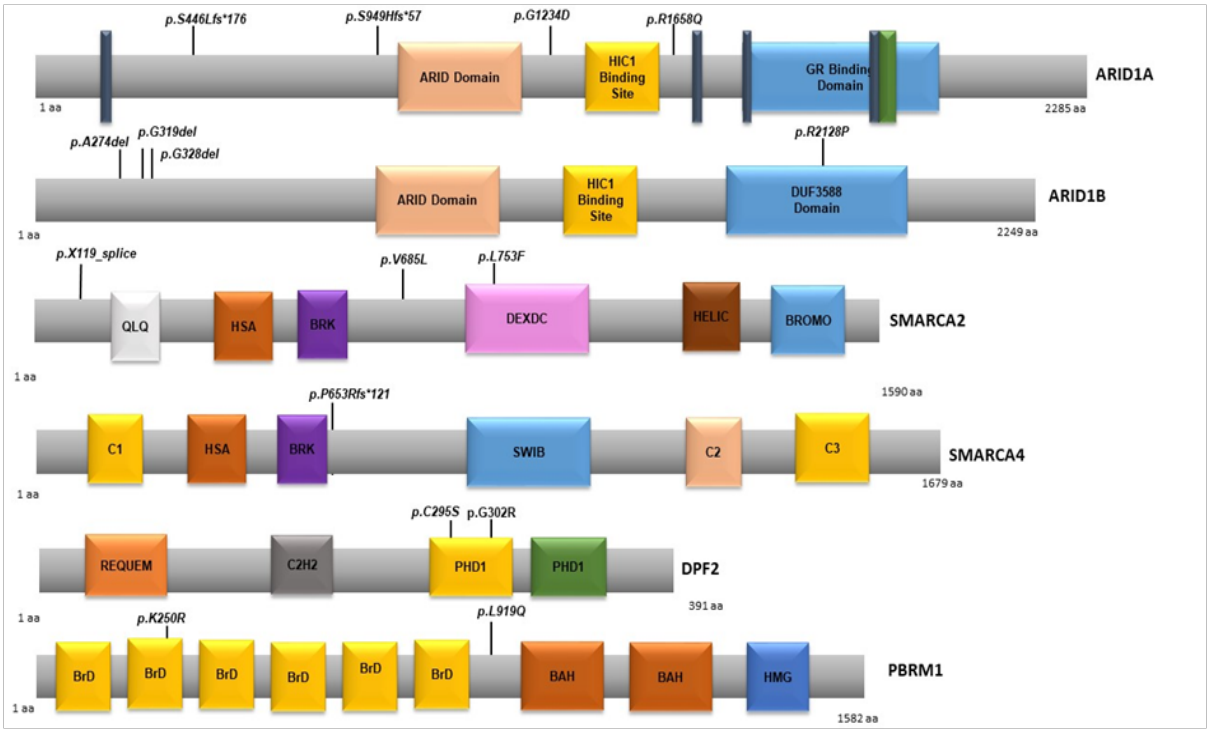

Figure 2: Schematic representation of domain architecture of the ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, and, PBRM1 proteins and mutations identfied in patients with AML. Human ARID1A is a polypeptide comprising 2285 amino acids. Human ARID1B is a polypeptide comprising 2249 amino acids. Human SMARCA2 is a polypeptide comprising 1590 amino acids. Human SMARCA4 is a polypeptide comprising 1679 amino acids. Human DPF2 is a polypeptide comprising 391 amino acids. Human PBRM1 is a polypeptide comprising 1582 amino acids.

compared to the control group (p<0.01) (Figure 2B). Our survival analysis based on low and high gene expression levels revealed that the expression levels of the genes had no significant impact on the overall survival (OS) of AML patients.

Analysis of the protein-protein interaction

STRING analysis was performed to detect the interactions of ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1 and BCL7A proteins in cellular processes. As shown in Figure 3, our target

Table 2. Detailed mutations of the *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1*, and *DPF2* in AML patient.

No	*Gene*	Nt alteration	Rs Number	Mutation Type	Localization	AA position	Type of Cancer	Pathogenic/Oncogenic Feature		
								Poly-Phen2 (score)	SIFT (score)	Mutaion Assesor (score)
M-1	*ARID1A*	c.1332_1333del	NA	Frame Shift Deletion	Exon-2	S446Lfs*176	AML with inv(16) (p13.1q22) or t(16;16) (p13.1;q22); *CBFB-MYH11*	NA	NA	NA
M-2	*ARID1A*	c.2845_2846del	NA	Frame Shift Deletion	Exon-9	S949Hfs*57	AML	NA	NA	NA
M-3	*ARID1A*	c.4973G>A	COSV61377605	Missense mutation	Exon-18	R1658Q	APL with *PML-RARA*	Probably Damaging (0.99)	Deleterious (0.00)	Low (1.70)
M-4	*ARID1A*	c.3701G>A	NA	Missense mutation	Exon-14	G1234D	AML	Possibly Damaging (0.90)	Deleterious (0.00)	Low (1.75)
M-5	*ARID1A*	-	NA	Fusion	-	ARID1A-RPS6KA1 Fusion	AML	NA	NA	NA
M-6	*ARID1B*	c.942_944del	NA	Frame Shift Deletion	Exon-1	G319del	APL with *PML-RARA*	NA	NA	NA
M-7	*ARID1B*	c.821_823del	NA	Frame Shift Deletion	Exon-1	A274del	AML with Minimal Differentiation	NA	NA	NA
M-8	*ARID1B*	c.983_985del	NA	Frame Shift Deletion	Exon-1	G328del	AML, NOS	NA	NA	NA
M-9	*ARID1B*	c.6383G>C	NA	Missense mutation	Exon-20	R2128P	APL with *PML-RARA*	Probably Damaging (1.00)	Deleterious (0.00)	Mediun (2.73)
M-10	*SMARCA2*	c.356-2A>T	NA	Splice region mutation		X119_splice	AML	NA	NA	NA
M-11	*SMARCA2*	c.2053G>T	NA	Missense mutation	Exon-14	V685L	AML	Probably Damaging (0.98)	Deleterious (0.03)	Mediun (2.00)
M-12	*SMARCA2*	c.2257C>T	COSV61812998	Missense mutation	Exon-15	L753F	AML with Mutated *NPM1*	Probably Damaging (1.00)	Deleterious (0.00)	High (3.94)
M-13	*SMARCA4*	c.1958del	NA	Frame Shift Deletion	Exon-13	P653Rfs*121	AML	NA	NA	NA
M-14	*DPF2*	c.883T>A	COSV52889333	Missense mutation	Exon-8	C295S	AML with Mutated CEPBA	Probably Damaging (1.00)	Deleterious (0.00)	High (3.74)
M-15	*DPF2*	c.904G>A	NA	Missense mutation	Exon-8	G302R	AML with Mutated NPM1	Probably Damaging (1.00)	Deleterious (0.00)	Mediun (3.29)
M-16	*PBRM1*	c.749A>G	NA	Missense mutation	Exon-8	K250R	AML	Probably Damaging (1.00)	Tolerated (0.19)	Neutral (0.66)
M-17	*PBRM1*	c.2756T>A	NA	Missense mutation	Exon-18	L919Q	AML	Benign (0.00)	Tolerated (0.42)	Low (1.25)

Abbreviations: M: Mutation; NA: Not available; Nt: Nucleotid; Rs: Register; AA: Amino acid; Inv: Inversion: t: translocation

genes SMARCA4, SMARCE1 and SMARCB1 interact with the PHF10 protein.

DISCUSSION

The SWI/SNF complex is involved in the homeostasis of hematologic processes, and mutations in the SWI/SNF subunits are thought to contribute to the development or progression of hematologic malignancies. There fore, the mutation and expression profiles of our target genes, namely *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A*, were detected in detail using the genome sequencing data of 872 adult patients diagnosed with AML from the TCGA. Among the 17 mutations identified in a total of 9 genes in the 872 AML patients, there were 9 missense, 6 frameshift mutations, 1 mutation in the splice region and 1 fusion. *ARID1A* was found to be the most frequently mutated gene, while *SMARCE1* and *BCL7A* had no mutations. *ARID1A* is the most frequently mutated subunit in SWI/SNF complexes, with mutations occurring in approximately 8% of cancers. Mutations that render SWI/SNF subunits ineffective are found in approximately 20% of cancers, suggesting that proper function of this complex is necessary to prevent tumor formation in various tissues.[2,10,14,15,16] However, mutations of the SWI/SNF complex are rarely detected in AML compared to other hematologic cancers and solid tumors. This suggests that the complex may not exert a significant tumor suppressor function for this malignancy.[7,12,14,15,24] *ARID1A* and *SMARCA4* play a role in both myeloid and lymphoid differentiation, regulate erythropoiesis and are involved in granulocytic maturation.[7,10,25,26] *ARID1A* is located on 1p36, a chromosomal part that is frequently deleted in tumors, and it is known that nonsense and frameshift mutations in the gene lead to a loss of function.[27] The two frameshift mutations (p.S446Lfs176 and p.S949Hfs57) that we identified in the AML cohort are driver mutations and may contribute to the loss-of-function phenotype. The ARID1A-RPS6KA1 fusion variant we discovered as a structural variant encompasses the *RPS6KA1*, which encodes a member of the ribosomal S6 kinase family of serine/threonine kinases. Many RTKs are known to play an active role in cancer development due to chromosomal translocations, and this pathological condition is also referred to as overexpression for short.[28] In our AML cohort, the expression level of *ARID1A* is higher compared to the healthy group, which might be due to the structural variant ARID1A-RPS6KA1.ARID1B protein has only two identified domains: AT-Rich Interactive Domain (ARID) and Domain of Unknown Function 3518 (DUF3518). DUF3518 is approximately 260 amino acids lenght, and this domain is known to interact with the helicase subunits BRG1 and BRM in BAF complexes.[28,29] In our study, the p.R2128P mutation was determined on the DUF3518 domain, and therefore it is likely that these missense mutations interrupt the interaction between *ARID1B, BRG1*, and *BRM*. *ARID1A* and *ARID1B* have been defined as tumor suppressor genes involved in chromatin remodeling, epithelial-mesenchymal transition, and many other cellular and molecular processes.[29-31] However, their role in AML has not yet been clarified. The molecular mechanisms related to *ARID1B* mRNA expression appear to be different in different cancer tumors.[32] In our AML cohort, *ARID1B* expression levels were higher compared to the healthy group. Considering the tumor suppressor nature and the need to elucidate the molecular mechanism, this suggests that *ARID1A* and *ARID1B* may not act as tumor suppressors specifically in AML.

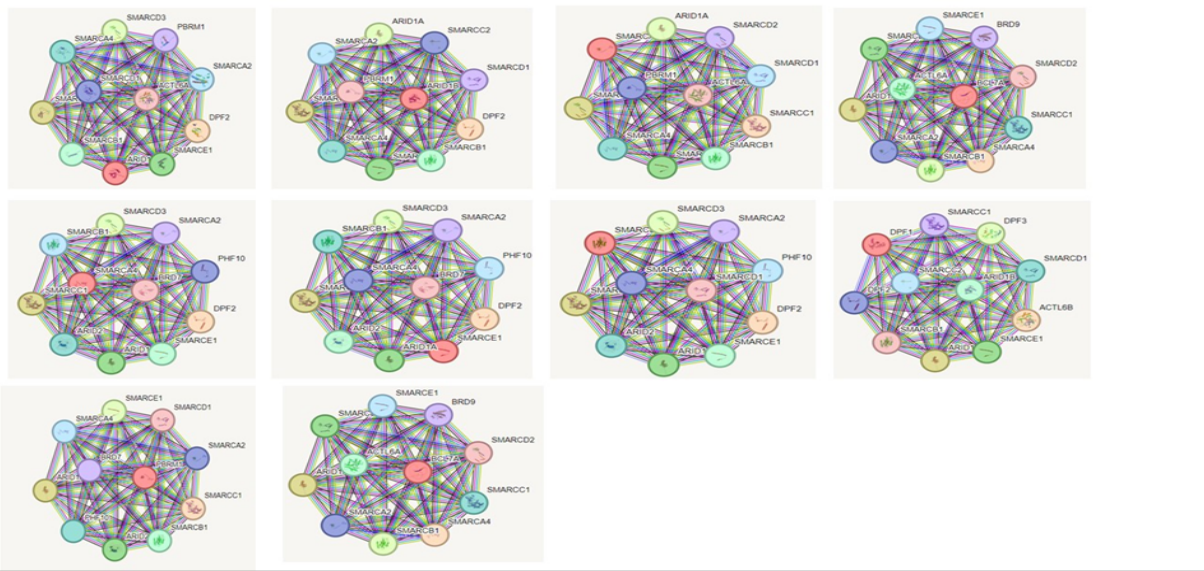

Figure 3: Schematic representation of known and predicted protein-protein interactions with the ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1, and BCL7A proteins.

SMARCA2 has been shown to process the telomerase reverse transcriptase (TERT) gene and modulate the splicing mechanism of *TERT*. Since *TERT* activation is thought to be cancer-promoting, SMARCA2 is not thought to have a tumor suppressive function.[33-34] We believe that the p.V685L and p.L753F mutations we discovered in the SNF2 ATPase domain of *SMARCA2* may have a dominant-negative effect by eliminating the

ATP-hydrolyzing motor potential of the protein, thereby abrogating its ability to reposition histones on DNA. The p.X119_splice mutation we identified on the same gene is oncogenic in nature and typically results in loss of protein function of *SMARCA2*. The *SMARCA4* encodes the BRG1 protein, which belongs to the SWI/SNF family of proteins responsible for remodeling chromatin to regulate transcription of multiple genes.[34-36] The frameshift mutation p.P653Rfs*121, which we discovered in *SMARCA4*, is a loss-of-function mutation that causes the polypeptide to break prematurely, resulting in a truncated protein. Recent studies have shown that mutations in the ATPase domain of *SMARCA4*, which we also identified, do not repress the Polycomb Repressive Complex (PRC)-1 from chromatin and result in loss of accessibility of enhancers.[33-35] *SMARCA4* also modulates the expression of CD44 and the function of MYC and can interact directly with the tumor suppressor gene BRCA1.[33-36] Upregulation of *SMARCA4* in tumor tissues is related with aggressive tumors, whereas upregulation of *SMARCA2* is associated with well-differentiated tumors, suggesting that *SMARCA4* and *SMARCA2* have opposite roles in tumor tissues.[37,38] In this study, the expression levels of *SMARCA4* did not differ from those of the control group, whereas *SMARCA2* had high expression levels in our AML cohort, suggesting that it may be a prognostic indicator for AML. In addition, the *SMARCA2* amplification identified in our study could also be a source of increased expression levels.SMARCA2 mutations can contribute to the development of new therapeutic strategies in the treatment of AML because these mutations can affect patients' response to treatment and the course of the disease.[6,7,36-38]Firstly, AML patients with SMARCA2 mutations may develop resistance to certain drugs or have reduced response to specific treatments. This can decrease the effectiveness of traditional treatment regimens and necessitate the exploration of alternative treatment options.[37,38] However, detected mutations in current study also provide an opportunity for the development of targeted therapies. For example, drugs or therapeutic agents targeting specific vulnerabilities associated with SMARCA2 mutations can be developed. This allows for the design of treatments that target the specific biological pathways affected by the mutation, potentially leading to better responses to treatment in AML patients with SMARCA2 mutations. As more information is gathered about the impact of this mutations on AML treatment, there is potential to develop more effective and personalized treatment options.

The *PBRM1* encodes BAF180, a protein that serves as a DNA target subunit of the pBAF SWI/SNF complex and contains six bromodomains. These bromodomains, particularly the one affected by the p.K250R missense mutation in our study, have the ability to recognize acetylated residues at histone tails, indicating a pathological nature that could disrupt histone-histone interactions. Bromodomains have the ability to recognize acetylation patterns and target the entire complex to specific chromatin regions.[39-41] *PBRM1* is known to be involved in DNA repair mechanisms. It facilitates DNA double-strand break repair, transcriptional silencing and maintenance of centromeric cohesion, which is critical for maintaining genomic stability.[6,40,41] The p.K250R mutation detected in our study may disrupt these interactions. Interestingly, our study showed that *PBRM1* has high mRNA expression in the AML cohort, suggesting an oncogenic role in contrast to its tumor suppressive role in other tissues. This highlights the complex role of *PBRM1* in different contexts and provides fundamental information for further research. The PBRM1 gene is a subunit of the SWI/SNF complex and can influence gene expression by regulating the structural organization of chromatin.[39-41] There fore, mutations in the PBRM1 gene are thought to potentially play a role in the prognosis of AML.

DPF2 is mutated in various cancers, including AML, lymphoma, and ALL, and the mutations frequently occur at hot-spot mutation sites, including PHD domains and the N-terminal region.[42] PHD domains are critical for reading post-translational modifications. The PHD domain is a structure that includes the ability of proteins to recognize and bind to histones. Therefore, the role of the PHD domain in the DPF2 gene in AML may influence histone modifications and consequently the ability to regulate gene expression. In our study, missense mutations (p.C295S and p.G302R) were detected in the PHD1 domain of *DPF2*. In particular, the Cys295 residue is critical for histone modifications. The ability of *DPF2* to bind to histones is necessary for the in vivo regulatory function of Hematopoietic stem/progenitor cells (HSPCs) in myeloid differentiation, and the detected mutations could affect histone modification.[42] In addition, the patient carrying this mutation also exhibits the RUNX1-RUNX1T1 translocation. Recent studies have shown that the inclusion of *DPF2* in a repressive complex containing *RUNX1* prevents the expression of RUNX1 target genes, including the myeloid-specific miR-223, and prevents myeloid distinction.[43]

In STRING protein-protein interaction analysis, the core proteins (hub proteins) SMARCA4, SMARCE1, and SMARCB1 interact with the protein PHF10, a subunit of the pBAF SWI/SNF complex that is required for its association with chromatin.[44] PHF10 protein has been reported to be required for proliferation of mouse neuroblasts and maintenance of transcriptional activation in hematopoietic progenitors and myelogenesis. Studies have shown that mice in which PHF10 protein has been knocked out die in the late stages of embryogenesis, and the surviving animals exhibit hematopoietic defects.[44]

Many studies have described the crucial functions of many SWI/SNF subunits, such as ACTL6A, ARID1A, ARID2, PBRM1, PHF10, and SMARCA2 for the maintenance of hematopoietic stem cells.[6-8,45] Specifically, SWI/SNF complexes can also interact with hematopoietic-specific transcription factors, including EKLF, RUNX1, PU.1, IKAROS, GATA1, and CEBPα.Increasing evidence has reported that mutations in SWI/SNF complex confer resistance to a variety of antineoplastic agents routinely used in the treatment of hematological malignancies, including ibrutinib, venetoclax, doxorubicin, paclitaxel, or vinblastine.[6-8,45]

CONCLUSION

Independent studies on SWI/ SNF-targeting chemotherapeutic agents, as well as on the role of SWI/ SNF mutations in drug resistance and the creation of targetable synthetic lethalities in SWI/SNF defective tumors and the mutations we demonstrated in our study, are opening new paths for improving leukemia treatment that hold a promising future.Although we have performed comprehensive molecular profiling analyses of the SWI/SNF complex, a fundamental mechanism that may be responsible for AML pathogenesis, we are aware of certain limitations of our study. This is because this study was carried out with a limited experimental design using bioinformatics tools. There fore, a wet laboratory study and a larger sample group are needed to clarify the effect of *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A*, on AML pathogenesis. Mutations and expression differences that we have discovered in SWI/SNF subunits can often create lethal synthetic relationships with other SWI/SNF or non-SWI/SNF proteins which could be therapeutically exploitable.As a result, we examined the molecular profiles of the *ARID1A, ARID1B, SMARCA2, SMARCA4, SMARCE1, SMARCB1, DPF2, PMBR1*, and *BCL7A* genes, which we conclude would be helpful in any in vivo-in vitro clinical trials that can provide solutions in the diagnosis and treatment of AML.

Ethics Committee Approval: The data used in our study were obtained from public database TCGA, therefore, ethical approval was not required.

Informed Consent: The data used in our study were obtained from public database TCGA, therefore, informed consent was not required.

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Author Contributions: Concept – DO, DFA; Design - DFA; Supervision - DFA; Data Collection and/or Processing - DFA; Analysis and/or Interpretation – DO, DFA; Literature Search – DO, DFA; Writing Manuscript – DO,DFA; Critical Review – DO,DFA.

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Katılımcı Onamı: Çalışmamızda kullanılan veriler TCGA kamuya açık veri tabanından elde edildiğinden hasta onamı gerekmemiştir.

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DETERMINATION AND APPLICATION OF FORECASTING METHOD FOR MEDICINE CONSUMPTION IN HEALTHCARE ORGANIZATION
SAĞLIK İŞLETMELERİNDE İLAÇ TÜKETİMİ İÇİN UYGUN TAHMİN YÖNTEMİNİN BELİRLENMESİ VE UYGULANMASI

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ABSTRACT

The aim of this research is to estimate the consumption of a selected medicine in a public hospital for the next 1-year period by choosing the most appropriate fore casting method. Kaptoril 5-mg tablets from January 2018 to December 2022 were examined. In this research, time series methods were applied to the existing data using the Minitab 18 program. Moving average, exponentials moothing, and Holt-Winters fore casting methods were used in this study. Error measures such as mean absolute error, mean absolute percent age error, and mean squared error were used to compare the methods. For Kaptoril 5 mg, the most appropriatedem and fore casting method according to error measures is the Multiplicative Holt-Winters Method. According to this method, the mean absolute percent age error is 37.23. According to the multiplic ative Holt-Winters model, the total medicine consumption in 2023 was found to be 145 tablets. This research shows that time series fore casting methods can be applied to help reliable decision making in stock management of medicines by making a sample application on a selected medicine in a public hospital.

Keywords: material management, pharmaceutical products, time series.

ÖZ

Bu araştırmanın amacı, bir devlet hastanesinde seçilen bir ilacın tüketiminin en uygun tahmin yöntemi seçilerek gelecek 1 yıllık dönem için tahmin edilmesidir. Araştırmada, 2018 yılı Ocak ayından, 2022 yılı Aralık ayına uzanan süreçteki 60 aylık Kaptoril 5 mg tablet için ilaç tüketim verileri incelenmiştir. Araştırmada Minitab18 programı kullanılarak mevcut verilere zaman serisi yöntemleri uygulanmıştır. Araştırmada talep tahmin yöntemlerinden hareketli ortalama, üstel düzeltme, Holt -Winters yöntemleri kullanılmıştır. Yöntemlerin karşılaştırılmasında ortalama mutlak hata, ortalama mutlak hata yüzdesi ve hata karelerinin ortalaması gibi hata ölçütleri kullanılmıştır. Kaptoril 5 mg için hata ölçütlerine göre en uygun talep tahmini yöntemi Çarpımsal Holt-Winters yöntemidir. Bu yönteme göre ortalama mutlak yüzde hata değeri 37.23'dür. Çarpımsal Holt-Winters modeline göre 2023 yılında toplam ilaç tüketiminin 145 olacağı bulunmuştur. Bu araştırma, bir devlet hastanesinde, seçilen bir ilaç üzerinde örnek uygulama yapılarak, ilaçların stok yönetiminde güvenilir olarak karar vermeye yardımcı olacak zaman serisi tahmin yöntemlerinin uygulanabileceğini göstermektedir.

Anahtar kelimeler: malzeme yönetimi, eczacılıkla ilgili ürünler, zaman serisi.

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INTRODUCTION

In health institutions, it is possible to ensure that the service delivery is not interrupted, and when the need for materialarises, it can be provided in the desired amount, at the desired time, in quality, and economically thanks to the correct material management.[1] Most of the good srequired to be kept in health institutions are quite expensive and can deteriorate in a short time. There is a risk of obsolescence of these products. Keeping excessive stocks brings burdens such as storage and personel costs and prevents the efficient use of resources.[2]

Health institutions must use their resources effectively and efficiently to provide uninterrupted service. Medical supplies constitute the item with the highest weight after personel expenses in health institutions.[3] Material planning using demand forecasting methods provides cost savings.[4] It is thought that health managers have an important role in this regard. Health managers should be able to use, analyze, and infer data. They should be able to use the data they have obtained to make predictions for the future.[5]

In the studies where fore casting methods are applied in health institutions, demand fore casting studies are conducted in which the number of patients, such as out patient fore casting, the number of surgeries, and the number of in patients, is estimated using the Holt method, trend analysis, moving average, Random Forest Regression method, Box-Jenkins method.[6-9] In addition, studies using Holt-Winters, regression, moving average and exponentials moothing and regression analysis on materials management, such as drugs, surgicalgauze used in intensive care, injectors, and medical supplies such as medicines.[3,4,10,11]

Fore casting methods can be used to avoid unnecessary or missing stocks in health institutions. This research aims to analyze the consumption of a selected drug in a public hospital using fore casting methods, to select the mostappropriate fore casting method according to the error criteria, and to predict drug consumption in the next 1-year period. This research will guide the selection of methods to be used in material planning in health institutions and more specifically in the selection of methods that can be used in the hospital pharmacy.

MATERIALS AND METHODS

The study was planned as a descriptive, single center study. In this study, the most appropriate estimation method was selected for the consumption of a selected drug in a public hospital, and drug consumption was estimated for the next 1-year period. The hospital is an AII group public hospital with 450 patient beds. In this study, moving average, exponentials moothing, and Holt -Winters fore casting methods were used. In this context, it is aimed to determine the most appropriate fore casting method. The values of error criteria such as Mean Absolute Error (MAE), Mean Absolute Error Percentage (MAEP), and Mean Square Error (MSE) were determined in measuring the accuracy of the fore casting results and comparing the methods to decide on the most appropriate method.[12]

In this study, 60-month Captopril 5 mg tablet drug consumption data for the period from January 2018 to December 2022 were analyzed. This drug was selected because it is included in the WHO essential drug list and is used in the treatment of cardiovascular diseases. Captopril 5 mg is a drug that helps lower blood pressure and is used for treating high blood pres sure (hypertension), heart failure, and heart attack (myocardial infarction).[13]

In the research, time series methods were applied to the available data using the Minitab 18 program. The time series method is the results observed in periods such as daily, weekly, or monthly. The time series method aims to determine the expected behavior in the future by explaining the trend of the variable in the past years. Using the past values of the observations in the series, future values can be estimated.[5]

As the data included a ready dataset and secondary data, this study did not require approval from an ethics committee or informed consent. Institutional permission was obtained from the hospital management for the implementation of the study (13.06.2023/217776859).

Examination of the Assumptions

Using the 3 and 5-month moving average method, if there are obvious trends or seasonality in the time series data, the simple moving average may not capture these patterns. This assumption was tested by trend analysis. In the single exponentials moothing method, appropriate selection of the weight parameter is important. This selection was made by trialand error. Forthe Holt-Winters method, the data setmust be stationary. This as sumption was examined using the Augmented Dickey-Fuller Test. Inaddition, normality was determined by the Jarque-Bera test; the auto correlation as sumption was tested graphically.

RESULTS

To determine which fore casting methods can be successful in the research, trend analysis was performed using the Minitab 18 program. In the trend analysis graph in Figure1, the x-axisrepresents months and the y-axisrepresents drug consumption. According to the trend analysis, it was determined that drug consumption was not constant but decreased in certain months and increased in certain months. Based on the years, it was determined that consumption showed a decreasing trend in the summer and an increasing trend in the winter.

In the analysis performed according to the 3-month moving average method to determine the drug requirement, the MAPE value was 39.3 and the MAD

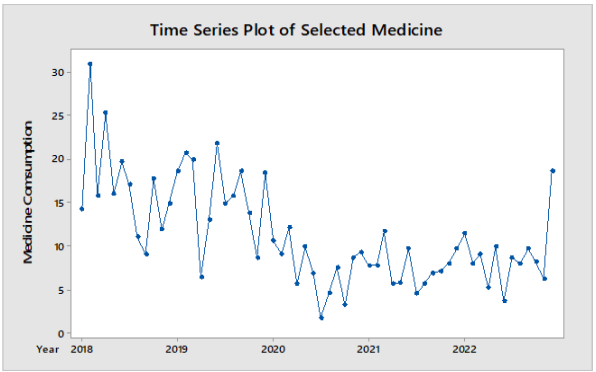

Figure 1: Trend Analysis

value was 3.22. In the analysis performed according to the 5-month moving average method to predict future drug consumption, the MAPE value was 43.8 and the MAD value was 3.3 (Figure2). The error rate increased as the number of months included in the moving average increased.

In the simple exponentials moothing method, the drug consumption estimation with correction coefficient α=0.8 has shown in Figure 3. When the correction coefficient is α=0.8, the MAPE value is 45 with a MAD value of 4.

As a result of the analysis, MAPE in the additive Holt-

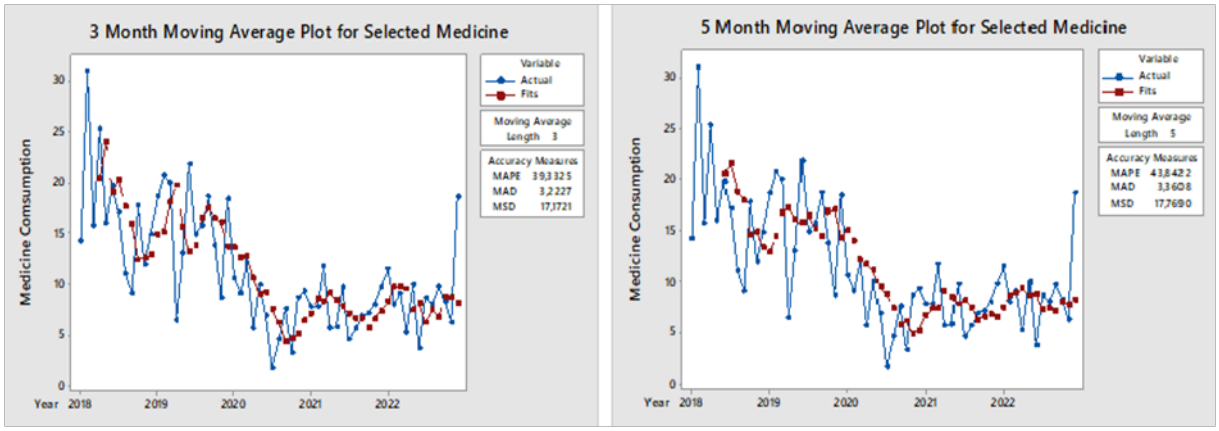

Figure 2: 3 and 5 Month Moving Average Graphs

In the simple exponential correction method, drug consumption was estimated with correctionco efficients α=0.2, α=0.5, and α=0.8. When the correctionco efficient was α=0.2, the MAPE value was 41.2 and the MAD value was 3.6 (Figure 3). In the simple exponentials moothing method, the drug consumption estimation with correction coefficient α=0.5 has shown in Figure 3. When the correction coefficient α=0.5, the MAPE value is 41.2 and the MAD value is 3.6.

Winters model was 37.25 and MAD was 3.51, where as MAPE in the multiplicative model was 37.23 and MAD was 3.5. The model with the lowest error rate was found to be the additive Holt-Winters model (Figure 4).

Table 1 shows the mean absolute percent age error (MAPE), mean absolute error (MAE), and means quare error (MSE) values, i.e., error measures, obtained at the end of the demand fore casting methods applied for pharma ceutical consumption.

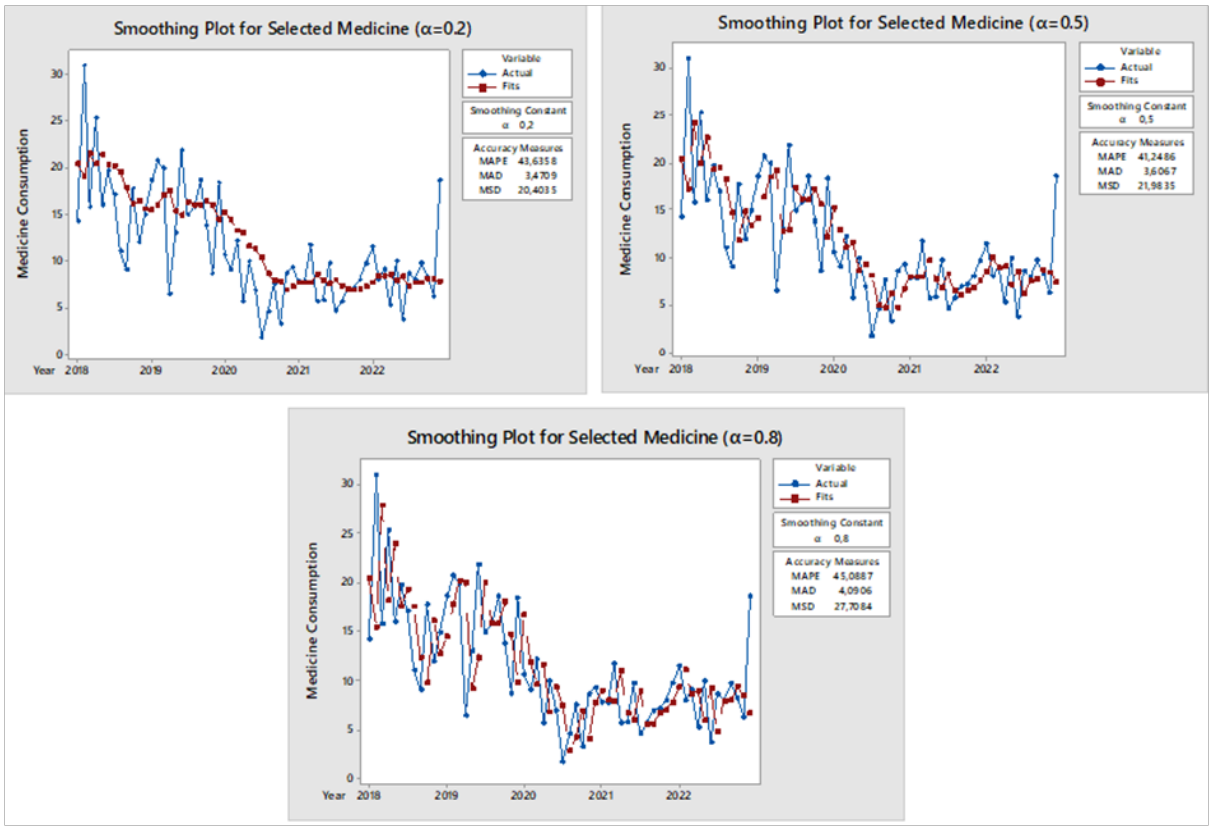

Figure 3: Simple Exponential Smoothing Method Graphs (α=0.2; α=0.5; α=0.8)

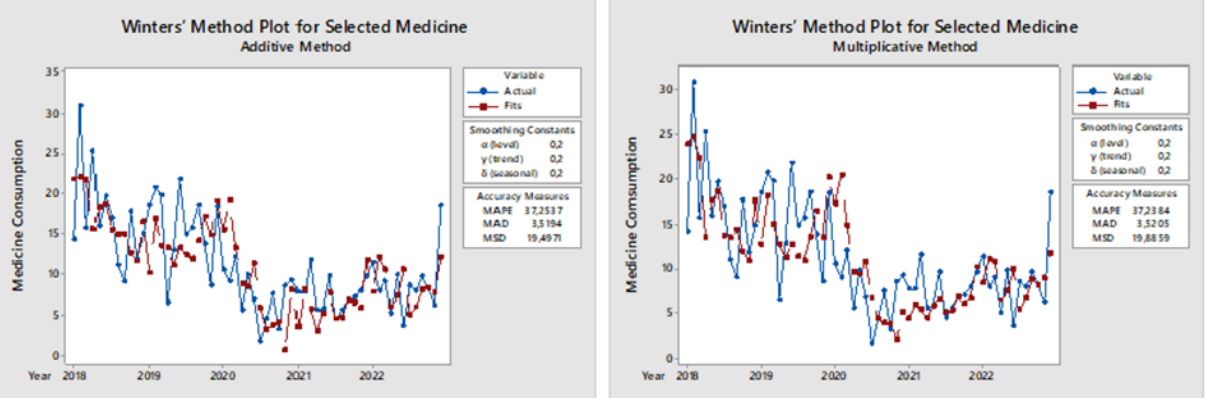

Figure 4: Additive and Multiplicative Holt-Winters Method Graphs

The most appropriate demand estimation method for captopril 5 mg according to the error criteria is the Multiplicative Holt-Winters Method. According to this method, the MAPE value is 37.23 (Table 1). MAPE allows the comparison of results obtained from different models applied to different time series. This statistic represents the average of the absolute differences between the predicted and observed values as a percent age. A small MAPE value indicates a model that fits the data well.[14] If the MAPE value is less than 10%, the prediction is considered to be highly accurate, where as if the value is more than 10% and less than 20%, it is considered to be a good prediction. If it is greater than 20% and less than 50%, the prediction is acep table, and when the MAPE is greater than 50%, the prediction is considered in correct.[15]

As a result of the comparison, future 12-month drug consumption was estimated (Table 2). According to the multiplicative Holt-Winters model, the total drug consumption in 2023 was found to be 145 tablets.

DISCUSSION

The health sector is a sector that deals with human life, it also stands out in the service sector. Managers have a great responsibility to ensure effective material management in hospitals. Uninterrupted and effective provision of health services is also an indicator of development levels.[16] Materials management in health

Table 1. Error Criteria According to Methods

Methods	*OMHY (MAPE)*	*OMH (MAE)*	*HKO (MSE)*
3 Month Moving Average	39.33	3.22	17.17
5 Month Moving Average	43.84	3.36	17.17
Single Exponential Correction (0,2)	43.63	3.47	20.40
Single Exponential Correction (0,5)	41.24	3.60	21.98
Single Exponential Correction (0,8)	45.08	4.09	27.70
Summative Holt-Winters Method	37.25	3.51	19.49
Multiplicative Holt-Winters Method	37.23	3.52	19.88

Table 2. 1-Year Drug Consumption Fore cast for the Future

Term	*3 Month Moving Average*	*5 Month Moving Average*	*Single Exponential Smoothing (0,2)*	*Single Exponential Smoothing (0,5)*	*Single Exponential Smoothing (0,8)*	*Summative Holt-Winters Method*	*Multiplicative Holt-Winters Method*[a]
Jan.2023	11.01	10.15	9.90	12.96	16.20	10.96	11.74
Feb.2023	11.01	10.15	9.90	12.96	16.20	13.37	12.92
Mar.2023	11.01	10.15	9.90	12.96	16.20	13.25	13.67
Apr.2023	11.01	10.15	9.90	12.96	16.20	9.38	8.56
May.2023	11.01	10.15	9.90	12.96	16.20	11.71	11.40
June.2023	11.01	10.15	9.90	12.96	16.20	13.08	12.06
Jul.2023	11.01	10.15	9.90	12.96	16.20	11.18	9.58
Aug.2023	11.01	10.15	9.90	12.96	16.20	11.48	10.24
Sep.2023	11.01	10.15	9.90	12.96	16.20	13.39	12.82
Oct.2023	11.01	10.15	9.90	12.96	16.20	13.20	11.59
Nov.2023	11.01	10.15	9.90	12.96	16.20	12.63	11.90
Dec.2023	11.01	10.15	9.90	12.96	16.20	18.81	19.24
Total	132.20	121.82	118.88	155.62	194.43	152.49	145.78

[a:] The most appropriated emand fore casting method.
The unit of medicine is a tablet.

services consists of the selection, procurement, distribution, and use of there sources required to provide health services, such as medicines and equipment. Materials management ensures that the limited resources in health institutions are used most appropriately and that the negative consequences of the deficiency are minimized. If material management is not done correctly, there is overor under-stocking.[17]

In this study, 5-year consumption data of Captopril 5 mg, which is used for treating cardiovascular diseases and included in the WHO essential drugs list, were analyzed and 12-month consumption for the future was estimated. According to the trend analysis, it was determined that drug consumption is not constant, it shows a decreasing trend in summer months and an increasing trend in winter months. It is thought that the decreasing drug consumption trend in the summer months is generally because fewer patients apply to hospitals for treatment in the summer months.

In this study, to determine the most appropriate fore casting method among the moving average, exponentials moothing, and Holt-Winters fore casting methods, the most appropriate method was found to be the Multiplicative Holt-Winters Method when the values of error criteria such as Mean Absolute Error (MAE), Mean Absolute Error Percentage (MAEP), and Mean Square Error (MSE) were analyzed. According to the multiplicative Holt-Winters model, total drug consumption in 2023 was found to be 145 tablets. Sarı and Gül applied time series methods to 36-month sales data of a domestic drug. In their research, they used ARIMA, exponentials moothing, artificial neural networks, and the Holt-Winters method. They found that the method that gives the best fore casting result is the integrated ANN model.[18] Uçakkuş and Koçyiğit used moving average, Holt-Winters method, and exponentials moothing methods in their research, in which they estimated surgical gauze consumption in intensive care and found that the method with the least error rate was the moving average method.[4] Özüdoğru and Görener applied moving average, exponentials moothing, Holt-Winters method, and regression analysis to predictsyring econsumption from medical supplies in a hospital in Istanbul. They found that the most appropriate method is the 5-month moving average method.[12]

Bon and Nganalyzed the consumption of Panadol 650 mg for 68 month susing different methods such as moving average, single exponentials moothing, double exponentials moothing, regression, additive Holt-Winters, multiplicative Holt-Winters, and ARIMA and found that regression analysis was the best prediction method.[19]Mbonyinshut et al. Analyzed the top ten most used essential medicines; cotrimoxazole 480 mg, amoxicillin 250 mg, paracetamol 500 mg, oral rehydrationsalts 20.5 g, chlorpheniramine 4 mg, nevirapine 200 mg, aminophylline 100 mg, artemether 20 mg+lumefantrine (AL) 120 mg, and cromoglycateophthalmic based on consumption data between 2015-2019. Linearregression, artificial neural network, and random forest from machine learning applications were used to predict future trends in the demand for essential medicines in Rwanda. Random forest could predict with 88 percent accuracy. The Random Forest model performed well as a fore casting model for the demand for essential medicines.[20]

The data of this research covers the period from January 2018 to December 2022. These dates coincide with the COVID-19 out break. The impact of the COVID-19 on medicine consumption has been examined by researchers. Gimbach et al. Examined the impact of the COVID-19 pandemic on attention deficithy peractivity disorder (ADHD) medication consumption. They found that ADHD medication consumption decreased in 2020 but increased as of 2021.[21] Vukićević et al. Found that the COVID-19 pandemic in Croatiaca used an increase in the consumption of antipsychotics, anxiolytics, hypnotics and tranquilizers, and anti depressants.[22] Barrett et al. Found reductions in the prescribing of ACE inhibitors, beta-blockers, calcium channel blockers, statins, antiplatelet, antithrombotics, ARBs, loopdiuretics, doxazosin, bendroflumethiazide, nitrates, and indapamide after the pandemic began (March-October 2020).[23] It is also use fultoconsider that the medicine examined in this research is used for treating high blood pres sure (hypertension), heartfailure, and heart attack (myocardial infarction). Mathieu et al. Stated that the pandemic and related measures had a significant impact on the decrease in theuse of cardiovascular and antidiabetic medicines in France, and that this was due to the decrease in treatments during the quarantine.[24] The medicine consumption examined in this research also tended to decrease in the following years compared to 2018 and 2019. The COVID -19 may have had an impact on this decrease.

Accuracy is an element that contributes to planning. Analyzing periodic consumption data to estimate the demand for pharmaceutical spharmaceuticals is important for making predic table decisions for the future. As a result, costsavings will be achieved in pharmaceutical supply and storage activities. Tomakestrategic decisions in the pharmaceutical sector, pastperiod data can be analyzed and fore casts for future consumption can be used. Thus, the risk of being affected by fluctuations in drug prices and the difficultiesen countered in drug storage in health institutions can be reduced and productivity can be increased.[18] Keeping the right amount of stock in health institutions means not incurring inventory holding costs and beingable to respond to health demand.

CONCLUSION

Health institutions have different categories of products, such as medicines, medical consumables, cleaning products, and stationery materials. Because medicines are products that arevital to be supplied as soon as they are needed, needto be stored in appropriate conditions, and have expiry dates, it is important to determine the consumption of medicines for the future. In the study, the most appropriate method was found to be the Multiplicative Holt-Winters Method. According to the method, the total medicine consumption in 2023 was found to be 145 tablets.

As a result of this research, by making a sample application on a selected medicine in a state hospital, time series fore casting methods can be applied to help reliable decision-making in the inventory management of medicines. It is recommended that these methods

should be used in the hospital pharmacies as decision support systems to help the mavoidover stock or under stock problems and improve inventory management.

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EVALUATION OF SATISFACTION WITH HOSPITAL MEALS, NUTRITIONAL STATUS AND HOSPITAL ANXIETY IN INDIVIDUALS WITH CARDIOVASCULAR DISEASE
KARDİYOVASKÜLER HASTALIĞA SAHİP BİREYLERİN HASTANE YEMEKLERİNDEN MEMNUNİYETİ, BESLENME DURUMU VE HASTANE ANKSİYETESİ DURUMUNUN DEĞERLENDİRİLMESİ

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ABSTRACT

This study was planned and conducted to examine the relationship between satisfaction with hospital meals, nutritional status and hospital anxiety in individuals with cardiovascular diseases. This cross-sectional and descriptive study was conducted with patients receiving treatment in the cardiology clinic between October 2021 and October 2022. The nutritional status of the patients was evaluated with the Nutrition Risk Screening-2002, their satisfaction with hospital meals with the Hospital Food Services Patient Satisfaction Scale, and their anxiety and depression status with the Hospital Anxiety and Depression Scale. In addition, 24-hour food consumption records and anthropometric measurements were taken. The study was completed with a total of 152 participants, 85 males and 67 females. The mean score of the satisfaction with hospital food services scale was 81.50 ± 15.02, 17.8% (n=27) of the participants had anxiety and 32.9% (n=50) had depression. Patients at risk of malnutrition were less satisfied with hospital food services and had higher levels of anxiety ($p<0.05$). In addition, it was observed that anxiety scores decreased as individuals' satisfaction with hospital meals increased. In conclusion, it was observed that satisfaction with hospital food services was associated with patients' malnutrition risk and anxiety level. Therefore, it should be aimed to prevent hospital malnutrition and improve the mental health of patients by increasing satisfaction with hospital food services.

Keywords: Anxiety, depression, hospital food services, malnutrition.

ÖZ

Bu çalışma kardiyovasküler hastalıklara sahip bireylerin hastane yemeklerinden memnuniyeti, beslenme durumu ve hastane anksiyetesi arasındaki ilişkinin incelenmesi amacıyla planlanıp yürütülmüştür. Kesitsel ve tanımlayıcı tipteki bu araştırma; Ekim 2021-Ekim 2022 tarihleri arasında kardiyoloji kliniğinde tedavi alan hastalarla yürütülmüştür. Hastaların beslenme durumu Beslenme Riski Taraması-2002, hastane yemeklerinden memnuniyetleri Hastane Yiyecek Hizmetleri Hasta Memnuniyeti Ölçeği, anksiyete ve depresyon durumları ise Hastane Anksiyete ve Depresyon Ölçeği ile değerlendirilmiştir. Ayrıca hastaların 24 saatlik besin tüketim kayıtları ve antropometrik ölçümleri alınmıştır. Çalışma 85 erkek ve 67 kadın olmak üzere toplam 152 katılımcı ile tamamlanmıştır. Hastane yemek hizmetlerinden memnuniyet ölçeği ortalama puanı 81.50 ± 15.02 olarak belirlenmiş, katılımcıların % 17.8'inde (n=27) anksiyete ve %32,9'unda (n=50) depresyon bulguları olduğu tespit edilmiştir. Malnütrisyon riski altındaki hastaların hastane yemek hizmetlerinden daha az memnun olduğu ve anksiyete seviyelerinin de daha yüksek olduğu belirlenmiştir ($p<0,05$). Ayrıca, bireylerin hastane yemeklerinden memnuniyetleri arttıkça anksiyete skorlarının düştüğü görülmüştür. Sonuç olarak hastane yemek hizmetlerinden memnuniyetin hastaların malnütrisyon riski ve anksiyete seviyesi ile ilişkili olduğu görülmüştür. Dolayısıyla hastane yemek hizmetlerinden memnuniyeti arttırarak hastane malnütrisyonunu önlemek ve hastaların mental sağlığını iyileştirmek hedeflenmelidir.

Anahtar kelimeler: Anksiyete, depresyon, hastane yemek hizmetleri, malnütrisyon.

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INTRODUCTION

Adequate and balanced nutrition contributes significantly to the treatment process by reducing the risk of hospital malnutrition in patients receiving treatment in inpatient institutions. In patients with hospital malnutrition, the risk of infection increases, recovery time is delayed and hospital stay is prolonged. In addition, the increase in morbidity and mortality risk along with the cost of treatment is also noteworthy. Hospital malnutrition not only occurs due to disease and disease-related complications but is also affected by the quality of hospital food services.[1, 2]

The aim of the hospital food service is to provide patients with adequate and balanced nutrition by offering menus that are nutritious and appropriate to their medical nutrition therapy. In addition, food consumption of inpatients is considered a good indicator of their nutritional status and satisfaction with the food service.[3] Patient satisfaction is considered as an important step in fulfilling quality requirements in health services and nutrition services constitute one of the important components of this satisfaction.[2] The quality of hospital food service can be affected by many factors such as the taste, appearance, temperature, hygiene and attitude of the staff. In addition, patients' loss of appetite due to the change of environment and their difficulty in adapting to dietary meals prepared specifically for their diseases also negatively affect satisfaction with catering services.[1] In a study conducted in Brazil, plate waste in meals served to hospitalized patients was found to be 7.7% on average per week. It was also among the results of the study that women had a higher rate of plate waste than men.[4] In a study conducted with patients aged 65 years and older hospitalized in different wards of hospitals in Turkey, the satisfaction rate with hospital meals was 61.1%. While the amount of energy and protein consumed by the patients in the hospital was sufficient, it was determined that their fat and salt consumption was high.[5] In this study, it was observed that adequate energy and protein intake was realized with the improvement in the satisfaction rate, while not consuming the food served in hospitals due to the quality of the food not being at the desired level is shown among the causes of malnutrition.[6]In support of this data, a study conducted in hemodialysis patients reported that malnutrition inflammation scores decreased as food consumption increased.[7] In another study, it was reported that improving the quality of hospital catering services would increase the overall satisfaction level with catering services and, as a result, reduce the length of hospital stay. It has been reported that the reduction in the length of hospital stay contributes to the psychological well-being of individuals as well as financial gain.[8]

Malnutrition is associated with many clinical outcomes, including depression. Failure to monitor the nutritional status of patients and the resulting unwanted weight loss may lead to an increase in the rate of depression.[9] Various studies conducted with elderly patients in our country have also supported this conclusion and an increase in depressive symptoms has been reported as the malnutrition score increases.[10, 11] Among the results of a study conducted with cancer patients; it was found that with appropriate nutritional interventions, it may be possible to reduce the extent of depression in individuals and thus improve the quality of life and survival rates of patients. In addition, it was emphasized that hospital anxiety score was also high in cancer patients and this was associated with malnutrition.[12] In similar studies conducted with cancer patients, it was reported that depression and anxiety scores were high in patients receiving oncologic treatment and these scores increased in relation to malnutrition.[13,14] In a systematic review examining this relationship in individuals with anorexia nervosa, 7 studies were analyzed and it was reported that there were differences in the results of the studies. It was stated that more comprehensive studies examining the relationship between anxiety, depression and malnutrition are needed.[15]

Depression and anxiety are highly prevalent in individuals with cardiovascular disease and are associated with deterioration in clinical outcomes and increased health costs. It is emphasized that individuals with cardiovascular disease with depressive symptoms are at risk for recurrent cardiovascular events and mortality.[16]

Satisfaction with hospital meals has been shown to be among the causes of malnutrition and the relationship between malnutrition and depression and anxiety has been confirmed in various studies in the literature. However, there are no studies investigating these relationships in cardiovascular diseases. This study was planned and conducted to examine the relationship between satisfaction with hospital meals, nutritional status and hospital anxiety in individuals with cardiovascular diseases.

MATERIALS AND METHODS

Study Plan

This cross-sectional and descriptive study was conducted in the cardiology clinic of Erciyes University Hospitals between October 2021 and October 2022. The study population was defined as conscious patients older than 18 years of age receiving treatment in the cardiology clinic for cardiovascular disease; patients with loss of consciousness and/or communication problems and patients in the terminal period were excluded from the study. Taking the effects size (0.53) of the study by Abdelhafez et al.[17] as a reference, the G*Power 3.1 program's t-test menu yielded a sample size of 130 based on α=0.05, 1-β=0.85, and effect size 0.53. The study was completed with 152 participants.

For this study, approval was obtained from Erciyes University Clinical Research Ethics Committee with the decision number 2021/491 dated 07.07.2021. In addition, all individuals participating in the study were informed about the study and their written and verbal consent was obtained.

Data Collection

Demographic information of the individuals was obtained with the help of a questionnaire form; body weight, height, waist, hip and neck circumference measurements were taken by the researchers in accordance with the technique. Body mass index (BMI) [weight (kg)/height $(m)^2$] was calculated from the weight and height measurements. Body mass index was evaluated according to WHO adult classification.[18]

Nutritional Risk Screening (NRS)-2002 was used to screen the nutritional status of the patients. NRS-2002 is a two-part screening tool that scores the deteriora-

tion in the nutritional status of patients and the severity of their diseases. In the first part, the severity of the disease, weight loss in three months and decreases in food intake in three months are questioned. The second part of the form is continued in patients who answered 'yes' to any of the questions in the first part. In the second part, patients are evaluated in terms of nutritional deficiency and disease severity, and a total score is determined by adding 1 point to the score obtained when the patient is 70 years of age or older. Patients with a total score of 3 and above are considered at risk of malnutrition.[19] According to the study of Bolayir et al.[20] NRS -2002 was found as a valid screening tool to evaluate malnutrition risk in Turkish hospitalised patients.

The 24-hour food consumption records of the patients were taken, and their average daily energy and nutrient consumption was determined with the Nutrition Information System (BeBiS, Istanbul, 2017) program. While food consumption records were taken, the Food and Nutrition Photo Catalog was used to determine the amount of food consumed.[21]

The Hospital Food Services Patient Satisfaction Scale (HFPSS) was used to assess satisfaction with hospital meals. The Turkish validity and reliability of the scale was conducted by Ercan and Ok in 2018. The scale has five sub-dimensions and consists of a total of 20 questions. The questions in the scale are evaluated with a five-point Likert scale and it is reported that as the score obtained from the scale increases, the satisfaction level of patients with hospital food services increases.[22]

The Hospital Anxiety and Depression Scale (HADS) was used to determine the risk of anxiety and depression in patients and to measure the level of existing depression and anxiety. The validity and reliability study of the scale in our country was conducted by Aydemir et al.[23] The scale consists of a total of 14 questions and the assessment is based on a four-point Likert-type scale. Different questions are used in the evaluation of anxiety and depression sub-dimensions and the total score of the scale is obtained by summing the sub-dimension scores. As a result of the study conducted in Turkey, a cut-off score of 10/11 was found for the anxiety subscale and 7/8 for the depression subscale. Accordingly, those above these scores were considered to be at risk.[24]

Statistical Analysis of Data

The data of the study were evaluated using the Statistical Package for Social Sciences for Windows (SPSS 22.0). In addition to the Shapiro-Wilk test, kurtosis and skewness value of the data were assessed to determine whether they were suitable for normal distrubition.[25]Numerical variables with normal distribution were expressed as "mean±standard deviation" and numerical variables without normal distribution were expressed as "median (minimum value-maximum value)". Categorical variables were expressed as "number (n)" and "percentage (%)". Independent sample t test was used to compare the normally distributed data between two independent groups, and One-Way Analysis of Variance (ANOVA) was used to compare the data between more than two groups. Kruskal-Wallis test was used to compare non-normally distributed data between more than two groups. When numerical variables were compared between groups, the Bonferroni test was applied for equal variances and the Tamhane T2 test for non-equal variances in pairwise comparisons. In all statistical analyses, $p<0.05$ was accepted as a significant value.

RESULTS

Table 1 shows the HFSPSS, anxiety and depression scores of the participants according to their general characteristics. The study was completed with a total of 152 participants, 85 men and 67 women. It was determined that 52% (n=79) of the participants were 65 years of age or older, 80.9% (n=123) were married, 54.6% (n=83) had four or more children, 59.9% (n=91) had high school or middle school education, and 42.1% (n=64) were housewives. According to the Hospital Anxiety and Depression Scale, 17.8% (n=27) of the participants had anxiety and 32.9% (n=50) had depression. According to the occupational status of the participants, the mean HFSPSS score showed a significant difference, and it was found to be higher in retired people (84.91±13.33) than in other occupational groups (75.29±15.15) (p=0.016). The mean anxiety score was higher in women (6.49±5.49), those with four or more children (6.30±5.39), illiterates (7.82±6.30), housewives (6.90±5.40) and non-alcohol users (5.94±5.27) ($p<0.05$). Mean depression score was higher in women (6.73±4.60), housewives (6.95±4.54) and smokers (8.35±5.55) ($p<0.05$).

Table 2 shows the comparison of mean HFSPSS, anxiety and depression scores according to the nutritional status of the participants. The mean HFSPSS score was found to be lower in patients who underwent the "main assessment" (76.05±16.86), which is the second step in NRS-2002, than in patients who underwent "only preliminary assessment" (83.38±13.93) (p=0.008). The mean anxiety score was found to be higher in individuals with a NRS 2002 baseline score of 3 and above (8.88±5.95) compared to those with a score of less than 3 (4.71±5.24) ($p<0.05$). There was no significant difference in mean HFSPSS, anxiety and depression scores according to BMI and neck circumference classifications *(*$p>0.05$).

Anxiety and depression scores, anthropometric measurements and nutrient intakes of the patients according to HFSPSS score quartiles are shown in Table 3. Anxiety score showed a significant difference according to the HFSPSS quartiles and this difference was found to be caused by the difference in the mean values of Q_1 (6.64±5.33) and Q_2 (3.31±3.38) (*p=0*.031). There was no significant difference between quartiles in anthropometric measurements (*p>0*.05). Among the daily intake of nutrients, a significant difference was found only in vitamin K intake level between the quartiles, and this difference was found to be due to the difference between Q_1 [45.40-(Min-Max: 1.50-487.85)] and Q_2 [96.50 -(Min-Max: 1.50-954.20)], Q_1 [45.40-(Min-Max: 1.50-487.85)] and Q_3 [90.50-(Min-Max: 3.60-471.74)] and Q_2 [96.50-(Min-Max: 1.50-954.20)] and Q_4 [45.50-(Min-Max: 0.00-521.52)] ($p<0.05$).

DISCUSSION

The aim of this study was to evaluate the satisfaction with hospital meals, nutritional status and hospital anxiety status of individuals with cardiovascular dis-

Table 1. Evaluation of HFSPSS, anxiety and depression scores according to the general characteristics of the participants

	n (%)	HFSPSS Score (x̄ ± SD)	Anxiety Score (x̄ ± SD)	Depression Score (x̄ ± SD)
Gender				
Male	85 (55.9)	81.49 ± 14.64	4.44 ± 4.75	5.17 ± 4.90
Female	67 (44.1)	81.52 ± 15.61	6.49 ± 5.49	6.73 ± 4.60
Total	152 (100.0)	81.50 ± 15.02	5.34 ± 5.17	5.86 ± 4.81
		t=-0.011, p=0.991	t=-2.416, **p=0.017**	t=-1.995, **p=0.048**
Age (years)				
< 65	73 (48.0)	79.69 ± 15.77	5.36 ± 5.37	6.06 ± 5.04
≥ 65	79 (52.0)	83.17 ± 14.20	5.32 ± 5.02	5.67 ± 4.62
		t=-1.431, p=0.155	t=0.048, p=0.962	t=0.507, p=0.613
Marital Status				
Married	123 (80.9)	81.21 ± 14.76	4.86 ± 4.70	5.73 ± 4.84
Single/Separated from spouse	29 (19.1)	82.75 ± 16.32	7.41 ± 6.54	6.37 ± 4.76
		t=-0.497, p=0.620	t=-1.983, p=0.055	t=-0.642, p=0.522
Number of Children				
< 4	69 (45.4)	81.36 ± 13.59	4.20 ± 4.68	5.43 ± 4.51
≥ 4	83 (54.6)	81.62 ± 16.20	6.30 ± 5.39	6.21 ± 5.05
		t=-0.108, p=0.915	t=-2.564, **p=0.011**	t=-0.996, p=0.321
Education Status				
Illiterate	29 (19.1)	82.79 ± 18.72	7.82 ± 6.30[a]	7.79 ± 4.59
Literate	11 (7.2)	80.18 ± 13.38	4.81 ± 4.53[a,b]	4.72 ± 3.31
Primary and secondary school	91 (59.9)	81.78 ± 14.27	4.96 ± 4.82[a,b]	5.54 ± 5.04
High school and above	21 (13.8)	79.23 ± 14.09	3.85 ± 4.4[b]	5.14 ± 4.29
		F=0.264, p=0.851	F=3.124, **p=0.028**	F=2.083, p=0.105
Profession				
Retired	61 (40.1)	84.91 ± 13.33[a]	4.01 ± 4.71[a]	4.73 ± 4.54[a]
Housewife	64 (42.1)	80.87 ± 15.78[a,b]	6.90 ± 5.40[b]	6.95 ± 4.54[b]
Other*	27 (17.8)	75.29 ± 15.15[b]	4.66 ± 4.79[a,b]	5.81 ± 5.58[a,b]
		F=4.093, **p=0.019**	F=5.449, **p=0.005**	F=3.407, p=0.036
Smoking				
Yes	14 (9.2)	82.21 ± 13.48	5.42 ± 6.71	8.35 ± 5.55[a]
Quitting	44 (28.9)	83.59 ± 16.10	4.18 ± 4.20	4.50 ± 4.65[b]
No	94 (61.8)	80.42 ± 14.76	5.88 ± 5.30	6.12 ± 4.63[a,b]
		F=0.678, p=0.509	F=1.632, p=0.199	F=3.923, **p=0.022**
Alcohol Use				
Yes	5 (3.3)	85.80 ± 1.59	0.00 ± 0.00[a]	3.00 ± 2.64
Quitting	19 (12.5)	85.52 ± 11.53	2.73 ± 3.28[b]	5.00 ± 3.88
No	128 (84.2)	80.74 ± 15.57	5.94 ± 5.27[c]	6.10 ± 4.97
		F=1.049, p=0.353	F=6.351, **p=0.002**	F=1.350, p=0.262
Anxiety				
Yes	27 (17.8)	79.11 ± 19.94	14.44 ± 2.72	10.96 ± 4.21
No	125 (82.2)	82.02 ± 13.78	3.38 ± 3.03	4.76 ± 4.20
		t=0.723, p=0.475	t=-18.746, **p<0.001**	t=-6.952, **p<0.001**
Depression				
Yes	50 (32.9)	78.90 ± 16.90	9.60 ± 5.22	11.68 ± 3.19
No	102 (67.1)	82.78 ± 13.93	3.26 ± 3.68	3.00 ± 2.18
		t=1.503, p=0.135	t=-7.694, **p<0.001**	t=-19.610, **p<0.001**

HFSPSS: Hospital Foos Service Patient Satisfaction Scale**Participants include civil servants, freelancers, workers and students.
t Independent sample t test, F One-way analysis of variance,[a,b,c] Post hoc. Different letters indicate a significant difference.

Table 2. Evaluation of HFSPSS, anxiety and depression scores of the participants according to nutritional status

	n (%)	HFSPSS Score (x̄ ± SD)	Anxiety Score (x̄ ± SD)	Depression Score (x̄ ± SD)
NRS First Evaluation				
Only preliminary assessment	113 (74.3)	83.38 ± 13.93	4.90 ± 4.85	5.47 ± 4.72
Main assessment	39 (25.7)	76.05 ± 16.86	6.64 ± 5.90	6.97 ± 4.97
		t=2.682, **p=0.008**	t=-1.821, p=0.071	t=-1.682, p=0.095
NRS Main Assessment Score				
< 3	21 (53.8)	75.85 ± 16.86	4.71 ± 5.24	6.23 ± 5.20
≥ 3	18 (46.2)	76.27 ± 17.34	8.88 ± 5.95	7.83 ± 4.68
		t=-0.077, p=0.939	t=-2.327, **p=0.026**	t=-0.999, p=0.324
BMI Classification (kg/m²)				
< 25.00	35 (23.0)	82.02 ± 13.85	5.00 ± 5.36	5.65 ± 5.03
25.00 - 29.99	55 (36.2)	78.92 ± 16.29	5.50 ± 5.64	6.01 ± 5.47
≥ 30.00	62 (40.8)	83.50 ± 14.38	5.40 ± 4.69	5.83 ± 4.08
		F=1.383, p=0.254	F=0.107, p=0.898	F=0.060, p=0.941
Neck Circumference				
Normal	30 (19.7)	77.93 ± 16.59	5.16 ± 5.22	5.26 ± 4.37
Risky	122 (80.3)	82.38 ± 14.55	5.39 ± 5.18	6.00 ± 4.92
		t=-1.459, p=0.147	t=-0.214, p=0.831	t=-0.754, p=0.452

HFSPSS: Hospital Foos Service Patient Satisfaction Scale
t Independent sample t test, F One-way analysis of variance

Table 3. Anxiety and depression scores, anthropometric measurements and nutrient intakes of the participants according to quartiles of the HFSPSS score

	Q_1 (0-73 points) (n=39) *($\bar{x}$ ± SD) / Median (Min-Max)*	Q_2 (74-83 points) (n=38) *($\bar{x}$ ± SD) / Median (Min-Max)*	Q_3 (84-95 points) (n=39) *($\bar{x}$ ± SD) / Median (Min-Max)*	Q_4 (96-100 points) (n=36) *($\bar{x}$ ± SD) / Median (Min-Max)*	F/H	*p*
Age (years)	62.92 ± 9.47	63.86 ± 13.03	66.41 ± 8.48	64.52 ± 10.91	0.754	0.521
Anxiety score	6.64 ± 5.33[a]	3.31 ± 3.38[b]	5.53 ± 5.51[ab]	5.88 ± 5.74[ab]	3.026	**0.031**
Depression score	6.76 ± 5.46	5.00 ± 4.14	6.79 ± 5.33	4.77 ± 3.83	2.000	0.117
Body weight (kg)[ʼ]	76.00 (52.00-148.00)	76.50 (46.00-125.00)	80.00 (48.00-110.00)	76.50 (50.00-104.00)	1.664	0.645
BMI (kg/m)[2] [ʼ]	28.08 (16.59-61.60)	26.88 (16.69-55.56)	29.13 (18.37-39.04)	29.78 (20.80-44.89)	1.096	0.778
Neck circumference (cm)	37.82 ± 4.05	37.50 ± 4.36	37.53 ± 2.44	38.00 ± 3.59	0.155	0.926
UMAC (cm)	29.75 ± 4.78	29.05 ± 5.14	29.10 ± 3.62	31.05 ± 3.93	1.641	0.182
Energy (kcal)	1367.18 ± 387.37	1451.79 ± 461.60	1432.58 ± 483.81	1434.36 ± 453.95	0.267	0.849
Protein (g)	57.61 ± 17.96	56.02 ± 18.72	57.01 ± 21.94	58.30 ± 23.77	0.081	0.970
Fat (g)	58.48 ± 19.57	65.34 ± 24.54	61.61 ± 23.56	57.32 ± 25.69	0.884	0.451
Carbohydrate (g)	147.64 ± 51.53	155.73 ± 53.57	157.65 ± 62.00	166.30 ± 53.08	0.720	0.542
Fiber (g)	14.64± 6.70	14.50 ± 5.75	17.11 ± 8.77	15.63 ± 7.63	1.052	0.372
Cholesterol (mg)	260.65 ± 163.93	269.37 ± 133.98	253.68 ± 156.60	210.69 ± 148.31	1.089	0.356
Vitamin A (µg)[ʼ]	621.00 (201.92-2634.55)	693.82 (140.16-4961.20)	835.50 (138.15-2538.87)	625.73 (0.00-1913.79)	5.134	0.162
Vitamin D (µg)[ʼ]	1.36 (0.20-4.03)	1.72 (0.13-8.07)	1.84 (0.10-10.44)	1.02 (0.00-4.28)	7.033	0.071
Vitamin E (mg)[ʼ]	4.86 (1.57-37.91)	5.03 (0.75-16.39)	4.70 (1.67-24.44)	4.56 (0.98-24.68)	1.369	0.713
Vitamin K (µg)[ʼ]	45.40 [a](1.50-487.85)	96.50 [b](1.50-954.20)	90.50 [bc](3.60-471.74)	45.50[acd](0.00-521.52)	9.149	**0.027**
Vitamin B_1 (mg)	0.68 ± 0.24	0.68 ± 0.27	0.74 ± 0.34	0.74 ± 0.37	0.377	0.770
Vitamin B_2 (mg)	1.32 ± 0.50	1.29 ± 0.54	1.27 ± 0.57	1.29 ± 0.66	0.035	0.991
Vitamin B_6 (mg)	0.93 ± 0.37	0.85 ± 0.37	0.93 ± 0.49	0.94 ± 0.45	0.341	0.796
Vitamin B_{12} (µg)	3.76 ± 1.92	4.00 ± 2.09	3.91 ± 2.40	3.47 ± 2.47	0.405	0.750
Folate (µg)	215.55 ± 97.51	220.51 ± 106.76	261.76 ± 147.67	234.62 ± 140.97	1.072	0.363
Vitamin C (mg)[ʼ]	77.39 (4.32-214.97)	62.96 (0.00-214.66)	72.11 (15.44-424.89)	71.23(0.00-256.03)	1.864	0.601
Sodium (mg)[ʼ]	2687.96 (713.55-8533.80)	3041.90 (628.00-4756.80)	2982.65 (738.00-6179.20)	3070.02 (555.00-5924.00)	3.329	0.344
Potassium (mg)	1912.99 ± 617.53	1887.65 ± 809.68	2018.24 ± 839.92	1951.07 ± 858.06	0.202	0.895
Calcium (mg)	742.41 ± 325.70	744.04 ± 348.23	687.80 ± 276.92	753.60 ± 365.13	0.315	0.815
Magnesium (mg)	199.08 ± 69.61	196.09 ± 77.42	201.07 ± 87.99	199.70 ± 80.40	0.027	0.994
Phosphorus (mg)	949.71 ± 316.34	947.96 ± 384.13	899.65 ± 359.37	931.82 ± 398.93	0.157	0.925
Iron (mg)	6.35 ± 2.74	6.58 ± 2.70	7.14 ± 3.46	6.83 ± 3.04	0.689	0.689
Zinc (mg)	8.08 ± 3.25	8.69 ± 3.74	8.96 ± 4.41	8.16 ± 3.96	0.462	0.709

HFSPSS: Hospital Foos Service Patient Satisfaction Scale, BMI: Body Mass Index, UMAC: Upper mid-arm circumference One-way analysis of variance,[ʼ]Kruskal wallis test,[a,b,c,d] Post hoc. Different letters indicate a significant difference.

ease. The results of the study showed that satisfaction with hospital food services was not affected by gender, age, marital status and educational status. Only retired patients were more satisfied with catering services compared to patients in other occupational groups. When anxiety and depression scores were evaluated; anxiety and depression scores of women and housewives were found to be higher than other patient groups (Table 1). In studies conducted on different populations, it has been determined that women have higher levels of depression and anxiety than men. Among the reasons for this situation, it was stated that learned helplessness, socioeconomic factors, inability to provide socialization at the desired level and emotionality.[26,27]

When the relationship between satisfaction with hospital food services and anxiety and nutritional status was evaluated, it was found that patients at risk of malnutrition were less satisfied with hospital food services and had higher levels of anxiety (Table 2). In another study conducted in our country with 109 patients, no significant relationship was found between malnutrition risk and general satisfaction with hospital food services. However, this was explained by the limitations in the sample size of the study and the length of hospital stay of the individuals; the need for new studies including more variables was emphasized.[28] In a study conducted in Iran, it was concluded that plate wastage due to dissatisfaction with food services was associated with hospital malnutrition; it was reported that this issue should be considered as an important health problem and appropriate strategies should be adopted.[29] In a systematic review published on the subject, the relationship between malnutrition and hospital meal satisfaction was emphasized; it was stated that caterers should improve the process with appropriate interventions, especially for at-risk groups.[30]

In various studies conducted with cancer patients, similar to the findings of our study, a significant relationship between malnutrition status and depression and anxiety scores was emphasized.[13,31] The relationship between malnutrition and depression was also confirmed in a study conducted in chronic hemodialysis patients.[32]In this study, it was determined that there was a relationship between malnutrition and anxiety in individuals with cardiovascular disease.

In our study, it was observed that anxiety scores decreased as individuals' satisfaction with hospital meals increased (Table 3). When this issue is examined in the literature, it is observed that the number of studies is limited. In a study conducted on the elderly, the general satisfaction of patients with hospital services was evaluated and depression was reported to affect the perceived quality of hospital care and satisfaction.[33]In a systematic review in 2019 that evaluated the factors affecting the satisfaction of elderly people with hospital food services, it was reported that there was no relationship between satisfaction with food services and mental health. However, this study also emphasized that more studies are needed to clarify this issue.[34]Our study will provide a new reference to the literature in this context.

CONCLUSION

In this study, satisfaction with hospital food services was associated with patients' malnutrition risk and anxiety level. Based on this result, it should be aimed to prevent hospital malnutrition and improve the mental health of patients by increasing satisfaction with hospital food services. In order to increase satisfaction with hospital catering services, it is important to improve the variety, taste, smell and freshness of meals that affect food quality. In addition, patients' preferences, perceptions, needs and complaints should also be taken into consideration.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Erciyes University (Date: 07.07.2021, Number: 2021/491).
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PARAMEDİK OLMAK İÇİN GEREKLİ ANTROPOMETRİK ŞARTLARIN, MESLEĞİN GEREKTİRDİĞİ FİZİKSEL YETERLİLİĞİ BELİRLEMEDEKİ ETKİSİ*

THE EFFECT OF THAT ANTHROPOMETRIC CONDITIONS REQUIRED FOR BEING A PARAMEDIC, DETERMINING THE PHYSICAL COMPETENCE REQUIRED BY THE PROFESSION

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ÖZ

İnsan faktörü, günümüz toplumlarında üretkenliğin veya hizmetin devam edebilmesinin ilk basamağıdır. Bu yüzden her açıdan iyilik hali tüm meslek grupları için incelenmesi gereken parametreler içerir. Bazı meslek grupları için fiziksel uygunluk, hem iş gücü kaybını önlemede hem de mesleklerin getirdiği zorlu fiziksel stresle başa çıkmada önemli bir noktadır. Paramedikler için de fiziksel uygunluk önemlidir. Paramediklerin çalışma alanında birçok noktada karşılaşılan fiziksel stresle başa çıkabilmesinin ilk adımı iyi bir fiziksel kapasiteye sahip olmaktır. Ülkemizde farklı dönemlerde paramedik adayları için antropometrik kriterler istense de, bu uygulamadan vazgeçilmiştir ve fiziksel kapasiteyi değerlendiren etkinliği ve güvenilirliği yüksek uygulamaların olmayışı bizi bu çalışmaya yöneltmiştir. Çalışmamızda antropometrik özelliklerin incelenerek paramedikler için fiziksel yeterliliği belirleyip belirleyemeyeceğinin tayini amaçlanmıştır.

Çalışma Giresun Üniversitesi, Şebinkarahisar Sağlık Hizmetleri Meslek Yüksekokulu'nda gerekli tüm izinler alındıktan sonra İlk ve Acil Yardım programı öğrencisi olan 113 kişi ile uygulanmıştır. Bu çalışmada katılımcıların boy uzunlukları ve vücut ağırlıkları belirlenmiş ve beden kitle indeksleri hesaplanmıştır. Fiziksel performans tayininde ise, paramedikler için fiziksel yeterlilik testi protokolü olan "Omni Life Support Paramedic Physical Ability Test" uygulanmıştır.

Çalışmaya göre, katılımcı popülasyonunda boy uzunluğunun daha fazla olması ($p<0.001$) ve vücut ağırlığının daha fazla olması ($p<0.001$) fiziksel kapasiteyi olumlu etkilemektedir. Bununla beraber belirlenen antropometrik sınırlar içerisinde olanlar ile antropometrik şartları sağlamayanlar arasında fiziksel yeterlilik testi sonuçları açısından anlamlı bir fark bulunamamıştır ($p>0,05$). Tek başına antropometrik verilerin değerlendirmeye alınmasının mesleki fiziksel yeterliliğin belirlenmesinde yeterli olamayacağı, belirleyiciliği daha hassas ölçüm yöntemlerine ihtiyaç olduğu ve ülkemizde uygulanabilir fiziksel yeterlilik testleri protokollerinin hazırlanması ve uygulanması gerektiği düşünülmektedir.

Anahtar kelimeler: Antropometri, insan faktörleri ve ergonomi, kardiyopulmoner resusitasyon, paramedik, vücut ağırlığı ve ölçüleri.

ABSTRACT

The human factor is the first step in the continuation of productivity or service in today's societies. There fore, well-being in every aspectin cludes parameters that should be examined for alloccupational groups. For some occupational groups, physical fitness is an important point both in preventing loss of work force and in coping with the challenging physical stress of occupations. The lack of highly effective and reliable applications that evaluate the physical capacity of paramedics led us to this study. In our study, it was aimed to determine whether it can determine physical competence for paramedics by examining anthropometric characteristics.

The study was carried out with 113 students of First and Emergency Aid program at Giresun University, Sebinkarahisar Vocational School of Health Services, after all necessary permissions were obtained. In this study, the height and body weights of the participants were determined and their body mass indexes were calculated. In the determination of physical performance, "Omni Life Support Paramedic Physical Ability Test", which is a physical aptitude test protocol for paramedics, was applied.

According to the study, greater height ($p<0.001$) and body weight ($p<0.001$) positively affectt hephysicalcapacity of the participant. However, there was nosignificant difference between those who are with in the determined anthropometric limits and those who do not meet the anthropometric conditions in terms of physical adequacy test results ($p>0.05$). It is thought that the evaluation of anthropometric data alone will not be sufficient to determine occupational physical competence, which requires more precise measurement methods, and that applicable physical adequacy test protocols should be prepared and implemented in our country.

Keywords: Anthropometry, human factors and ergonomics, cardiopulmonary resuscitation, paramedic, body weight and measurements,

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GİRİŞ

Ergonomi, birçok bilim dalı ile multidisipliner bir çalışma alanı oluşturur. Teknikleri ve yöntemleri açısından bazı branşlardan faydalanır, etkileri ve sonuçları bakımından ise bazılarını etkisi altına alır. Tüm bu olay örgüsü, iş hayatında insan sağlığının korunması ve işgücü kaybının önlenmesi ilkeleri doğrultusunda ergonomiye çalışma alanı oluşturur.[1]

Ergonomi biliminin faydalandığı en önemli yöntem bilimlerinden biri de antropometridir. Vücudun uzunluk, genişlik, çap gibi sayısal verilerini değerlendirerek sınırlarını keşfetmemizi sağlar. Tüm bu verilerin ışığında, ergonomi bilimi ise ortamın, araç-gereçlerin, kısacası hayatın insana uyumlu hale getirilmesini sağlar.[2,3] Tüm çalışanlarda olduğu gibi sağlık çalışanlarının da çalışma ortamlarında tam anlamıyla verimli olabilmeleri için ergonomi biliminin tüm imkânlarından faydalanmak gerekir. Çünkü günümüz iş hayatı sürekli dinamik, üreten, hizmet veren bir mekanizma olarak karşımıza çıkmaktadır.

Ülkemizde yakın tarihlerde gelişmeye ve ilerlemeye başlayan bir meslek grubu olarak paramedikler, sağlık çalışanları içerisinde iş sağlığı ve güvenliği açısından en riskli çalışma ortamına sahip meslek gruplarından biri olarak karşımıza çıkmaktadır.[4,5] Sözel-fiziksel şiddetin yanında, araç kazaları, kesici-delici alet yaralanmaları, vücut sıvıları ile direkt temas, kas iskelet sistemi sorunlarına kadar birçok yönden risk altındadır.[6] Sahip oldukları tüm teknik bilginin dışında paramedikler, iyi bir fiziksel yeterliliğe de sahip olmalıdırlar. Çünkü mesleğin gerektirdiği bazı zorluklar ancak iyi bir fiziksel dayanıklılık ve güç ile çözülebilmektedir.[7] Teknik ve mesleki bilginin dışında, iş ortamında maruz kalınan ve fiziksel olarak güç gerektiren; hasta taşıma, uzun süreli Kardiyopulmoner Resusitasyon (KPR) uygulamaları, ambulansa sedye yerleştirilmesi gibi birçok zorlu görev tanımlanmıştır.[8]

Bazı meslek gruplarının gerektirdiği zorlu fiziki şartlar, istihdamda dikkate alınarak değerlendirilmektedir. Fiziki yeterlilik, mesleki etkilenimi minimum düzeye çekmede, işgücü kaybını önlemede, sağlıklı bir iş hayatının oluşturulmasında, iş verimini ve kalitesini arttırmada başvurulan ilk yeterlilik testleri olarak düşünülebilir.[9] Bu testler kişilerin bazı işleri yapmasını engellemek adına olduğu düşünülmemelidir. Asıl amaçlanan kişilerin niteliklerine uygun işlere yönlendirilmesi olacaktır. Bunu "Bilir" kitabında "uygun işe yerleştirme" olarak anlatmaktadır.[2]

Bu çalışmanın amacı paramediklerde antropometrik özelliklerin fiziksel performansın üzerindeki etkisinin belirlenmesidir.

GEREÇ VE YÖNTEM

Çalışma tanımlayıcı araştırmadır. Örneklem seçilmemiş olup Giresun Üniversitesi, Şebinkarahisar Sağlık Hizmetleri Meslek Yüksekokulu İlk ve Acil Yardım bölümü öğrencilerinin tamamı (N=124) araştırmanın evrenini oluşturmaktadır.

Çalışma gerekli izinler alındıktan sonra, Giresun Üniversitesi, Şebinkarahisar Sağlık Hizmetleri Meslek Yüksekokulu bünyesinde İlk ve Acil Yardım bölümü öğrencileri ile, Helsinki Deklarasyonu prensiplerine uygun olarak ve tüm katılımcılardan bilgilendirilmiş gönüllü onam formu alınarak gerçekleştirildi (Etik kurul: KTÜ Tıp Fakültesi Bilimsel Araştırmalar Etik Kurulu No: 24237859-43, Giresun Üniversitesi Oluru: 15005096-000-E.14283 sayılı yazısı).

Çalışmaya evrenindeki 124 kişinin;

- Üç'ü bir gün öncesinden ağır antrenmana maruz kaldığı için,
- İki'si en geç bir hafta öncesine kadar kas-iskelet sistemi travmasına maruz kaldığı için,
- Üç'ü sistemik kronik kalp rahatsızlığı olduğu için,
- Üç'ü ise kronik astım hastası olduğu için çalışmaya dâhil edilmedi.

Çalışmaya katılan 113 katılımcı iki farklı çalışma grubuna ayrıldı. Birinci grup, 2018-2019 eğitim öğretim yılı ve öncesini kapsayan ve Ölçme Seçme ve Yerleştirme Merkezi'nin (ÖSYM) her yıl güncelleyerek yayınladığı "Tablo -3A, Tablo-3B, Tablo-4'te Yer Alan Yükseköğretim Programlarının Koşul ve Açıklamaları"nın 233. maddesine göre İlk ve Acil Yardım (İAY) programında eğitim alabilmek için gerekli olan antropometrik şartları sağlamayan adayların oluşturduğu gruptur.

Bu grubu;

- Boyu 160 santimetre (cm)'den kısa olan kadınlar,
- Boyu 165 cm'den kısa olan erkekler,
- Kilosu, boylarının santimetre cinsinden ifadesinin son iki rakamından 5 kilogram (kg)'dan fazlası olan bireyler,
- Kilosu, boylarının santimetre cinsinden ifadesinin son iki rakamından 15 kg'dan noksanı olan bireylerden oluşan toplan 53 kişiden (35 kadın, 18 erkek) oluşturdu.

İkinci grup ise gerekli antropometrik şartları sağlayan 60 kişiden (42 kadın, 18 erkek) oluşmakta idi.Katılımcı testleri Aralık 2019 – Şubat 2020 tarihleri arasında,kapalı spor salonunda ve haftasonu gerçekleştirildi.

Antropometrik Veriler

Bireylerin boy ve kiloları standart yöntemlerle ölçüldü.Boy uzunluğu ölçümleri standart bir mezuranın duvara sabitlenmesi ile yapıldı. Bireylerin pozisyonları ise; ayakları çıplak halde, ayaklar, kalça ve baş duvara yaslanmış şekilde, zemin ile baş tepe noktası arası mesafe okunarak kaydedildi. Vücut ağırlığı ise hassasiyeti 0.10 kg olan baskül ile katılımcılardan ayakkabıları ve ekstra ağırlık oluşturabilecek tüm elbiselerinin çıkarılması istendikten sonra göstergeden okunarak kaydedildi.[10]Beden kütle indeksi bireylerin ağırlıklarının kilogram cinsinden değerinin, boylarının metre cinsinden değerinin karesine bölünmesi ile kaydedildi (BKİ= kg/ m2).[11]

Paramedikler İçin Fiziksel Yeterlilik Testi Protokolü

Paramedikler adına belirlenen zorlu fiziki görevleri içeren "Omni Life Support's Paramedic Physical Ability Test" uygulandı. Test bir fizyoterapist eşliğinde gerçekleştirildi. Testten önce katılımcılara parkur hakkında eğitim verildi. Adayların 'Fiziksel Aktiviteye Hazırlık Anketi'ni dikkatlice okuyarak, dürüstçe 'HAYIR veya 'EVET' cevaplarını vermeleri istendi, yedi soruluk bu ankete soruların herhangi birisine 'EVET' cevabı verilmişse doktoruna danışmaları istendi.

Test hazırlığı için katılımcılardan rahat elbiseler ve spor salonunun zemini dikkate alındığında kaymaz kauçuk

tabanlı ayakkabı giymeleri, test günü hakkında önceden bilgi verilmiş ve iyice istirahat etmeleri, testten en az 2 saat öncesine kadar sigara içmemeleri, kafeinli içecekler içmemeleri ve ağır yemekler yememeleri istendi. Test öncesi alınan vital parametrelerde, nabzı 100 atım/dakika'dan hızlı olan katılımcılar ile kan basıncı 140 sistolik / 90 diastolik'ten yüksek olan katılımcılar test'e alınmadı, beş dakikalık bir dinlenim döneminden sonra vital parametreleri tekrar değerlendirildi. Değerler eğer bu parametrelerin üzerinde ise katılımcı teste dâhil edilmedi.

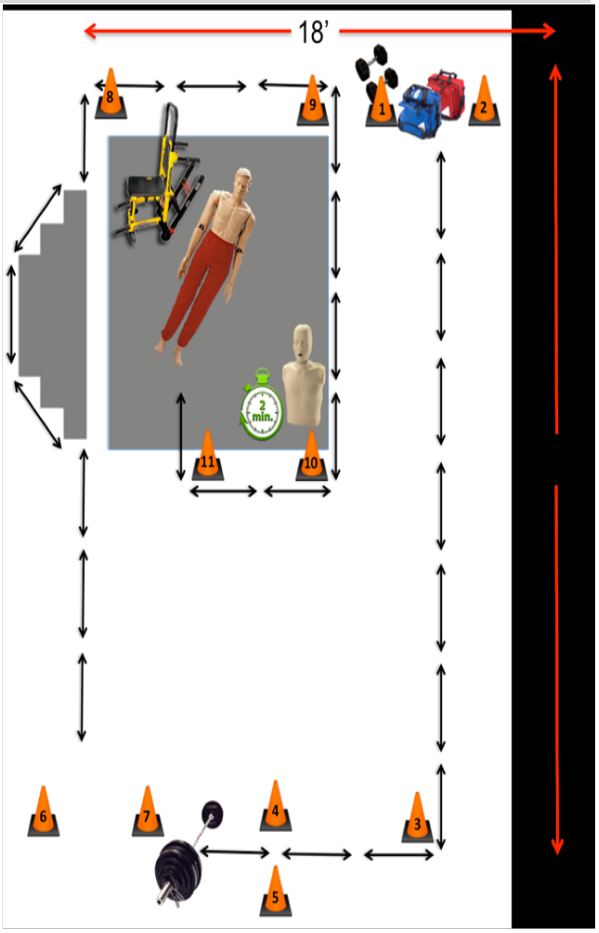
Parkur, bir hastanın evini kopya etmektedir ve paramedikler adına belirlenen zorlu fiziksel aktiviteleri içermektedir. Bu test 5 kademeden oluşmaktadır. Tedavi ekipmanlarının taşınması, iki dakika etkin kardiyopulmoner resüsitasyon, daha ağır ekipmanların taşınması, kombinasyon sedye ile merdiven inip-çıkma, hastanın travma tahtası veya faraş sedye ile ambulansa taşınması testin içeriğini oluşturmaktadır.

Ekipman Taşınması (1. basamak)

Ekipman çantalarının içerisinde standart malzemeler yer almaktadır ve ortalama 6 kg ağırlığındadır.1 ve 2 numaralı istasyonlardan başlayarak, 3-4 arasından, 5-6 arasından geçer ve merdivenlerden çıkar, iner, 7-8 arasından dönerek, 9-10 arasından simülasyon maketinin olduğu noktaya ulaşır.

KPR (2. basamak)

Sahada sıklıkla karşılaşılan bir uygulama olan KPR, parkurda zorluk derecesi yüksek bir bölüm olarak göze çarpmıştır. Bu bölüm, aralıksız, solunum uygulamaları olmadan sadece iki dakika boyunca etkin bir şekilde kalp masajı yapmayı içermektedir.



Daha Ağır Ekipmanların Taşınması (3. basamak)

Bazen olay yerinden ayrılıp ambulansa dönüp farklı ekipmanlar almak gerekebilir (ventilatör, aspiratör v.b). Bu basamak, bu durumu simüle etmek için kurgulanmıştır. Katılımcı KPR sonrası ekipman çantalarını alarak geldiği yoldan başlangıç noktasına geri döner. Yerdeki 11 kg'lık ağırlıkları alarak 10 numaralı istasyona geri döner.

Kombinasyon Sedye ile Hastanın Taşınması (4. basamak)

Türkiye İstatistik Kurumu (TÜİK) 2016 verilerine göre, erkekler için ortalama ağırlık 77.4 kg, kadınlar için 68.4 kg, toplam ağırlık ortalaması ise 72.8 kg'dır. Bu bölümde ortalama değerlere göre kombinasyon sedyenin üzerine 72 kg ağırlık yerleştirildi. Katılımcılar kombinasyon sedyeyi 10. İstasyondan alarak 9. 8. ve 7.istasyonu geçer, sedyeyi merdivene çıkarır ve merdivenden indirir. Bu süreçte minimal etki ve güç kullanımı ile sadece destek olmak amacı ile katılımcıya sedyenin merdivene çıkarılıp merdivenden indirilmesi için yardım edildi. Katılımcı sedyeyi 5. ve 6. İstasyonlar arasından geçirdikten sonra koyu yeşil renkli alana bırakmış ve bu bölüm tamamlanmıştır.

Bu uygulamada 37.5 kg halter kullanıldı. Bu ağırlık, bir travma tahtası üzerindeki standart ağırlıktaki hastanın, iki kişi ile taşınması esnasında kişi başına düşen yük miktarıdır. Katılımcı halteri kaldırır 3. ve 4. istasyon arasından geçerek başlangıç noktasına ulaşır. Geriye döner ve tekrar halteri aldığı noktaya getirerek yavaşça yere bırakır. Tam da bu noktada parkur bitmiştir. (Resim 1)

Katılımcılara parkuru bitirmeleri için 7 dakika süre verildi. Bu süre vakaya ulaşılan saat ile vakanın ambulansa alınıp hastaneye götürülmeye başlandığı saat arasında geçen ortalama süredir. Süre başladıktan sonra, katılımcı bitirene veya başarısız olana dek hiç durdurulmadı. Parkurun değerlendirilmesinde "BAŞARILI", "1" ve "BAŞARISIZ", "0" olmak üzere iki derece vardır.

Katılımcı herhangi bir nedenle testi yarıda bırakırsa, 7 dakika içerisinde bitiremezse, ekipmanları düşürürse, ekipmanları sert bir şekilde yere bırakırsa, testin herhangi bir basamağını yapmakta başarısız olursa test başarısız sayılır.

İstatistiksel Analiz

Verilerin analizi IBM SPSS 23 programı kullanılarak yapıldı. Tanımlayıcı tablolarda sayısal değişkenler ortalama, standart sapma, medyan, minimum ve maksimum değerleriyle kategorik değişkenler sayı (n) ve grup içindeki orantılarıyla (yüzde) verildi. Sayısal değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov ve Shapiro Wilk testi ile değerlendirildi. Normal dağılıma uyan sayısal değişkenlerin karşılaştırılmasında Student t testi, uymayanların karşılaştırılmasında Mann Whitney U testi kullanıldı. Kategorik değişkenlerin karşılaştırmasında Pearson Ki kare testi, beklenen değerin 5'in altında olduğu durumlarda Fisher's Exact test kullanıldı. İstatistiksel anlamlılık düzeyi $p<0.05$ olarak kabul edildi.

BULGULAR

Çalışmaya 113 kişi katıldı. Katılımcıların 77'si kadın(% 68.10), 36'sı (%31.90) erkekti. Katılımcıların yaşları 19

ile 22 arasında değişiklik göstermekteydi. Antropometrik kriterlere uygun olmayan katılımcı sayısı 53 kişiydi (%46.90). Bunların 35'i kadın, 18'i erkek katılımcı idi. Antropometrik şartlara uygun olan kişi sayısı ise 60 (%53.10) kişiydi. Bunların 42'si kadın ve 18'i erkek katılımcı idi (Tablo 1). Antropometrik uygunluk açısından bölünen gruplarda cinsiyet dağılımı açısından anlamlı bir fark bulunmadı (p>0.05).

Antropometrik açıdan incelendiğinde, katılımcıların boy uzunlukları 1.53 m ile 1.90 m arasında değişmekte idi [ortalama ve standart sapma (ort ± std. sapma):1.68±0.08]. Kilo ise 41 kg ile 100 kg arasında değişmekte idi (ort ± std. sapma:63.20±11.71). Katılımcılarda beden kitle indeksi(BKİ) 16.42 ile 34.31 arasında değişiyordu (ort ± std. sapma: 22.13±3.34) (Tablo 2).

Fiziksel Yeterlilik Testi Değerlendirmesi

Fiziksel yeterlilik testini incelediğimiz zaman, testi tamamlayamayan katılımcı sayısı 38 kişidir (%33.60). Bunların 37'si (%97,3) kadın ve sadece biri erkektir. Bu kişilerden 1'i (% 2.63) 1. basamakta, 3'ü (% 7.89) 2. basamakta, 5'i (% 13.15) 3. basamakta, 29'u (%76.31) 4. basamakta testi bırakmak zorunda kaldı. Beşinci basamağa gelip de testi tamamlayamayan katılımcı yoktu (Tablo 3).

Katılımcılarda cinsiyet ile fiziksel performans ölçeği ilişkisinin incelenmesinde, anlamlı fark olduğu saptandı (p<0,001). Kadınlarda 37 kişi (%48.10) fiziksel yeterlilik testinde başarısız olurken, erkeklerde bu sayı 1 kişi (%2.80) idi.

Önemli bir bulgu ise cinsiyetin fiziksel yeterlilik üzerine olan etkisinin BKİ skoru seviyelerine göre farklılık gösterdiğidir. Çalışma popülasyonunda BKİ skorlarına göre 11 kişi (% 9.70) zayıf, 83 kişi (& 73,50) normal kilolu, 16 kişi (% 14,20) fazla kilolu ve 3 kişi (%2,70) I. derecede obez olarak tespit edildi. Zayıf olan bireylerde (BKİ skoru < 18.50 kg/m2) ve I. derecede obez olan bireylerde (BKİ skoru 30-34.90 kg/m2 arasında) cinsiyetin fiziksel yeterlilik performansı üzerine etkisi istatistiksel olarak anlamlı değildi (Tablo 4).

ÖSYM'nin belirlediği antropometrik kriterlere göre katılımcıların fiziksel yeterlilik testinde başarılı veya başarısız olma durumlarını incelediğimizde, aralarında istatistiksel olarak anlamlı bir fark bulunamadı (p=0.09) (Tablo 5).

Tablo 1. Katılımcıların ÖSYM kriterlerine uygunluğunun cinsiyete göre dağılımı

		Cinsiyet				Toplam	%	p
		Kadın		Erkek				
		n	%	n	%			
Antropometrik uygunluk	**Uygun**	42	70	18	30	60	53.10	0.65
	Uygun değil	35	66	18	34	53	46.90	
	Toplam	77		36		**113**		

Tablo 2. Katılımcıların antropometrik özellikleri

	N	Ortalama	Standart sapma	Medyan	Minimum	Maksimum
Boy(m)	113	1.68	0.083	1.68	1.53	1.90
Ağırlık(kg)	113	63.20	11.71	61.00	41.00	100.00
Beden Kütle İndeksi	113	22.13	3.34	21.62	16.42	34.31

Tablo 3. Katılımcıların Fiziksel Yeterlilik Testindeki Kümülatif Başarı Durumları

	1. Basamak	2. Basamak	3. Basamak	4. Basamak	5. Basamak	Genel Toplam
Başarılı	112 (%99,10)	109 (% 97.30)	104 (% 95.40)	75 (% 72.10)	75 (% 100)	75 (% 66.40)
Başarısız	1	3	5	29	-	38
Bir Sonraki Basamağa Geçen Kişi Sayısı	112	109	104	75		

Tablo 4. Beden kitle indeksi gruplarına göre kadınlarda ve erkeklerde FYT başarı durumunun karşılaştırılması

		Fiziksel Yeterlilik Testi				Toplam	p
		Başarılı		Başarısız			
		n	%	n	%		
18,5 kg/m² den zayıf	**Kadın**	4	40	6	60	10	0.27
	Erkek	1	100	-	-	1	
18,5-24,9 arası normal kiloda	**Kadın**	32	56.10	25	43.90	57	**<0,001**
	Erkek	25	96.10	1	3.90	26	**<0,001**
25-29,9 arası fazla kilolu	**Kadın**	3	37.50	5	62.50	8	**0.009**
	Erkek	8	100	-	-	8	
30-34,9 arası I. Derece obez	**Kadın**	1	50	1	50	2	0.48
	Erkek	1	100	-	-	1	

Tablo 5. Katılımcıların, ÖSYM kriterlerine uygunluğu ile fiziksel yeterlilik testi başarı durumunun karşılaştırması

	Fiziksel Yeterlilik Testi				Toplam	p
	Başarılı		Başarısız			
	n	%	n	%		
Antropometik şartlara uygun	44	73.30	16	26.70	60	0.09
Antropometrik şartlara uygun değil	31	58.40	22	41.60	53	

Kişilerin boy uzunluklarının ve vücut ağırlıklarının dağılımına bakıldığında, başarılı olan kişilerin boy uzunlukları ($p<0.001$) ve vücut ağırlıkları ($p<0.001$) başarısız olanlara göre daha yüksekti ve bu durum istatistiksel olarak anlamlı idi (Tablo 6).

Tablo 6. Genel katılımcı popülâsyonunda boy uzunluğunun, fiziksel yeterlilik testi başarı durumu üzerine etkisinin karşılaştırması

	Fiziksel Yeterlilik testi	N	Ortalama	Standart sapma	p
Boy uzunlukları	**Başarılı**	75	170 cm	0.08	**<0,001**
	Başarısız	38	165 cm	0.56	
Vücut ağırlığı	**Başarılı**	75	65.32 kg	12.26	
	Başarısız	38	59.03 kg	9.36	

TARTIŞMA

Hastane öncesi acil sağlık çalışanlarının birçok araştırmada, ağır fiziksel stres altında oldukları belirtilmiştir.[5,12,13]Fischer ve arkadaşlarına göre, polis ve itfaiye gibi meslek grupları için, uygun işe yerleştirme (jobmatching) ilkesi doğrultusunda personel istihdamında farklı fiziksel standartlar uygulanmaktadır. Paramedikler adına belirlenen bir dizi zorlu fiziksel görev tanımlamasında sonra, acil sağlık hizmetleri çalışanları adına da fiziksel istihdam standartları getirilmesi gerektiğini savunmuşlardır.[8] Çalışmalar genelde fiziksel yeterlilik standartlarını iki amaç için kullanmayı öngörmüşlerdir. Birincisi; adayın işi yapabilecek fiziki kapasiteye sahip olup olmadığının tespitidir. İkincisi ise; çalışma süresince etkilenimi ve kas-iskelet sistemi yaralanmalarının öngörülebilmesi için kullanımıdır. Fakat paramedikler adına antropometrik verilerin fiziksel performansı belirlemede veya öngörmede kullanılıp kullanılamayacağını ortaya koyan benzer çalışmaların azlığı bizi bu çalışmaya yöneltmiştir.

Maguire ve arkadaşları acil sağlık hizmetleri çalışanlarının yaralanma riskinin, acil sağlık hizmetleri dışında çalışanlara oranla daha yüksek olduğunu belirtmiş, yaş ve cinsiyetin en önemli yaralanma faktörleri olduğunu söylemiştir. 25-34 yaş arasındaki kadın çalışanların en riskli grup olduğunu ortaya koymuştur.[14]

Jenkins ve arkadaşlarına göre; fiziksel uygunluk, paramedikler adına işyeri ortamındaki yaralanmalarda önemli bir parametredir ve bu parametre iş sonrası yaralanmaları öngörmede bize yol gösterici olabilmektedir. Bunun yanında paramedikler için işin kolay veya zorluğunu belirleyen parametreler ile yaralanmanın türü arasındaki ilişkiyi belirlemek için farklı çalışmalara ihtiyaç vardır.[15]

Çalışmamız doğrultusunda cinsiyet faktörünün fiziksel performans üzerine etkisinin önemi birçok çalışmada karşımıza çıkmaktadır. Bununla beraber gövdenin farklı bölgelerinde karşılaşılan hem kas kuvveti hem de kas hacmi açısından zayıf ekstremiteler, iş akışını bozacak önemli ölçütlerdir. Kennedy ve arkadaşlarına göre, zayıf üst ekstremite varlığı, çalışanlarda ilk yaralanma süresini kısaltmaktadır. Aynı zamanda kadınlarda, erkeklere oranla ilk yaralanma süresinin daha kısa olduğu gösterilmiştir.[16]

Çalışmamızda yaş faktörü incelemesi mümkün olmamıştır. Çünkü katılımcıların hemen hepsi aynı yaş aralığına sahip (19-22 yaş) bireylerden oluşmaktaydı. Gamble ve arkadaşları uzun süren vaka operasyonları sırasında paramediklerin kalp hızlarının anaerobik eşik değerin üzerine çıktığını, özellikle yaş ile beraber fiziksel kapasitenin azaldığını, bu durumun ambulans ekiplerinin seçiminde dikkate alınması gerektiğini, istihdam öncesi fiziksel standartların gerekliliğini ve erken emeklilik yaşının dikkate alınması gerektiğini savunmuştur.[17]

Ülkemizde istihdam adına uygulanan fiziksel kapasite tayininde kullanılabilecek herhangi bir ölçütün olmaması, atamalarda yapılan insan seçiminin işe uygunluğunu tartışır hale getirmiştir. Bu uygunluk bizi hem iş ile ilgili yaralanmalardan koruyacak bir değerlendirmeye götürür, hem de işgücü kayıplarının önüne geçmek için bize yol gösterici olabilir. Legge ve arkadaşları istihdam öncesi fonksiyonel kapasite değerlendirmesinin iş ile ilgili kas-iskelet sistemi yaralanmalarını öngörmek adına kullanılabileceğini belirtmişlerdir.[18]

Çeşitli ülkelerde paramedikler adına farklı standartlarda fiziksel kapasite testleri uygulanıyor olsa da, çalışmamızın özelinde Kanada'da uygulanan "Omni Life Support's Paramedic Physical Ability Test" için de cinsiyetler arasındaki farklılıkları belirleyebilecek bir çalışmaya ihtiyaç vardır. Zira Armstrong ve arkadaşları uygulanan fiziksel yeterlilik testlerinin cinsiyete dayalı farklılıklarının belirlenmesi gerektiğini belirtmişlerdir.[19]

Makhoul ve arkadaşları, kadınların fiziksel performanslarını arttırmak için alt beden kaslarından daha çok faydalanma eğiliminde olduklarını, çalışanların fiziksel kapasitelerini arttırabilmeleri için farklı taşıma stratejileri geliştirebileceklerini iletmiştir.[20]

Çalışmamızda cinsiyet faktörünün fiziksel yeterlilik üzerine etkisi ortaya konulmuştur. Bu durum beden kitle indeksi skoru çok düşük olan zayıf diyebileceğimiz bireylerde ve I. derecede obez kişilerde ortadan kalkmaktadır. Petersen ve arkadaşları da, kadın ve erkek arasındaki performans farklılıklarının antropometri ve cinsiyete dayalı güç ve endurans farklılıklarından kaynaklanabileceğini belirtmiştir.[21]

Roberts ve arkadaşları, boyun kadınlar ve erkekler arasındaki performans farkını oluşturabilecek bir antropometrik veri olabileceğini belirtmiştir. Boyun fiziksel performansı etkilediği gerçeği çalışmamız özelinde de kabul görmüş bir veridir. Fakat cinsiyetler arası incelendiğinde ne kadınlarda ne de erkeklerde boy uzunluğunun performansı etkilediğine dair bir istatistiksel veriye ulaşılamamıştır.[22]

Jaric ve arkadaşları vücut büyüklüklerinin performans testleri üzerine etkili olduğunu söylemiştir. Fakat farklı fiziksel performans testleri için farklı normalleştirme yöntemleri uygulanması gerektiğini belirtmişlerdir.[23] Çalışmamızda ise uyguladığımız fiziksel yeterlilik parkurunda, boy uzunluklarının ve ağırlığın performansı etkilediği, fakat beden kitle indeksinin performansı etkilemediği sonucuna varılmıştır.

Barnekow-Bergkvist ve arkadaşları, ambulans çalışanlarında yorgunluk gelişimine etki eden kriterleri değerlendirmiş, kilonun aksine boy ölçeğinin, kadın çalışanlarda yorgunluğun gelişimine etkisine dikkat çekmiştir.[24] Son dönemlerde ambulans hizmetlerinde çalışan kadın sayısındaki artış ile birlikte, fiziksel performans, vücut büyüklüğü ve yorgunluk gelişimi arasındaki ilişkinin kadın ve erkek çalışanlar adına ayrı ayrı araştırılmasının önemi anlatılmıştır. Fiziksel performans ve vücut ölçüleri arasındaki ilişkiyi değerlendirdiğimiz bu çalışmamızda; boy uzunluğunun ve vücut ağırlığının artışı ile fiziksel performansın iyileşmesinin örneklemde pozitif ilişkili olduğunu söyleyebiliriz. Fakat bu durum kadınlarda ve erkeklerde ayrı olarak cinsiyetler arasında incelendiğinde anlamlı fark olmadığı bulundu.

SONUÇ

Paramedikler adına fiziksel yeterlilik değerlendirme ölçütleri ülkemizde kullanılmamaktadır. Bu çalışmada geçmiş yıllarda uygulanan bir dizi antropometrik ölçeği değerlendirme fırsatı bulduk. İş ortamı ve yapılan mesleki uygulamalar göz önüne alındığında her meslek mensubunun minimal fiziksel yeterliliği karşılamasının, işin kalitesini arttıracağı düşünülmektedir.

ÖSYM'nin belirlediği antropometrik sınırların fiziksel performansı belirlemedeki etkisinin kısıtlılığı çalışmamızda görülmüştür. Antropometrik verilere dayandırılan beden kütle indeksi sınırlamalarının paramedikler için uygun bir işe yerleştirme kriteri olarak tek başına kullanılamayacağı düşünülmektedir. Antropometrik ölçülerin kullanılabilirliği mümkün olmakla beraber, bu ölçülerin belirlenmesinde, çalışma alanı olan ambulans araçlarının antropometrik verileri ile dönme ve uzanma gibi dinamik antropometrik değerlendirmeyi içeren çalışmalara ihtiyaç vardır.

Hem paramedik adaylarının hem de sahada aktif olarak çalışan paramediklerin, fiziksel performansı arttırmak ve fiziksel yeterlilik adına hazır bulunmaları için düzenli egzersiz alışkanlıkları edinmesi mesleki uygulamalar açısından faydalı olabilir.

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TÜRKİYE'DE PEDODONTİ (ÇOCUK DİŞ HEKİMLİĞİ) LİSANSÜSTÜ EĞİTİMİNDE TAMAMLANAN TEZLERİN İNCELENMESİ: METODOLOJİK BİR ÇALIŞMA

EXAMINATION OF THE THESES COMPLETED IN PEDODONTICS (PEDIATRIC DENTISTRY) POSTGRADUATE EDUCATION IN TÜRKİYE: A METHODOLOGICAL STUDY

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ÖZ

Bu çalışmanın amacı, Türkiye'de Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminde tamamlanan tezleri incelemek ve belirlenen kriterler doğrultusunda değerlendirmektir. Çalışma için Türkiye Ulusal Tez Merkezi'nde erişime açık olan ve 2012-2022 tarihleri arasında Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminde tamamlanan doktora ve uzmanlık tezleri incelenmiştir. Veriler istatistiksel olarak analiz edilmiştir. 293 doktora (%39.6) ve 446 uzmanlık tezi (%60.4) olmak üzere toplam 739 tez değerlendirilmiştir. En fazla tez 2022 yılında (133 tez, %18.0) ve en az tez 2012 yılında (32 tez, % 4.3) tamamlanmıştır. 700 tez (%94.7) devlet üniversitesinde ve 39 tez (%5.3) vakıf/özel üniversitede tamamlanmıştır. 636 tez (%86.1) kadın yazarlar tarafından yazılırken, 103 tez (%13.9) erkek yazarlar tarafından yazılmıştır. Tez danışmanlarının 160'ı doktor öğretim üyesi (%21.6), 194'ü doçent (%26.3) ve 385'i profesördür (%52.1). Tezler en çok çürük/koruyucu, restoratif ve protetik uygulamalar (306 tez, %41.4) ve en az ise yapay zeka/stres analizi/sonlu elemanlar (11 tez, %1.5) ve dudak damak yarığı/buruksizm/temporomandibular eklem rahatsızlığı (12 tez, %1.6) konusundadır. Laboratuvar çalışması/in vitro en çok kullanılan (286 tez, %38.7) ve bilgisayar tabanlı çalışma/in siliko (12 tez, %1.6) en az kullanılan metodolojidir. Ülkemizde uzmanlık eğitimin başlamasını takiben doktora tezlerinde azalma ve uzmanlık tezlerinde artış olduğu gözlenmiştir.

Anahtar kelimeler: Lisansüstü Eğitim, Pedodonti (Çocuk Diş Hekimliği), Tez

ABSTRACT

The aim of this study is to examine of the theses completed in Pedodontics (Pediatric Dentistry) postgraduate education in Türkiye and to evaluate them according to determined criteria. Doctoral (PhD) and master's (MSc) theses completed in Pedodontics (Pediatric Dentistry) postgraduate education between 2012-2022 years and accessible in the Türkiye National Thesis Center, were examined for study. The data were analyzed statistically. A total of 739 theses were evaluated, consisting of 293 doctoral (39.6%) and 446 master's theses (60.4%). The highest number of these were completed in 2022 year (133 theses, 18.0%), while the lowest number of these were completed in 2012 year (32 theses, 4.3%). Out of the total, 700 theses (94.7%) were completed at public universities, and 39 theses (5.3%) were completed at private universities. 636 theses (86.1%) were written by female authors, while 103 theses (13.9%) were written by male authors. 160 of these advisors were assistant professor doctor (21.6%), 194were associate professor (26.3%), and 385 were professor (52.1%). The theses mainly focused on topics such as caries/preventive, restorative, and prosthetic applications (306 theses, 41.4%), while the least focused topics were artificial intelligence/stress analysis/finite elements (11 theses, 1.5%) and cleft lip and palate/bruxism/temporomandibular joint disorder (12 theses, 1.6%). The most used methodology was laboratory study/in vitro (286 theses, 38.7%), while the least used methodology was computer-based study/in silico (12 theses, 1.6%). Following the start of master's education in our country, a decrease in doctoral theses and an increase in master's theses have been observed.

Keywords: Postgraduate Education, Pedodontics (Pediatric Dentistry), Thesis

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GİRİŞ

Pedodonti (Çocuk Diş Hekimliği), diş hekimliğinin tüm alanlarını kapsayan, çocuklar ve ergenler için hem koruyucu hem de tedavi edici bakımı sağlayan, yaşa göre özelleşmiş geniş bir uygulama alanı olan bilim dalıdır.[1,2] Ülkemizde bu alanda lisansüstü eğitim olarak hem doktora hem de uzmanlık eğitimleri verilmektedir.

Uzmanlık eğitimi çekirdek eğitim müfredatında çocuk diş hekimliğinin tanımı, "sağlıklı ve özel tedavi gereksinimi (zihinsel ve bedensel engelli bireyler, sistemik hastalığı olan bireyler) olan bebek, çocuk ve adölesanın büyüme ve gelişim dönemlerine göre süt ve genç daimi dişlerin ve çevre dokularının tedavi planlamalarının yapıldığı, davranış yönlendirmesi ile tüm diş hekimliği tanı, tetkik ve tedavilerini üstlenen erişkin diş hekimliğinden tümüyle ayrılan, kendine özgü konuları, sorunları ve yaklaşımı olan bir uzmanlık dalıdır" şeklinde yapılmıştır.[3] Çocuk diş hekimliği, literatürdeki güncel bilgileri kullanarak hastalara en son bilimsel gelişmeler ışığında tedavi olanakları sunmaktadır. Uzman hekimler genellikle mesleki deneyimlerden, yaygın klinik uygulamalardan, uzmanlık ve doktora eğitimlerinden, seminer ve kurslardan edindikleri bilgilerden yararlanarak tedavi kararlarını verirler. Aynı zamanda bu kararlarını verirken, doğrulanmış araçlardan elde ettikleri tıbbi literatürden de destek alırlar.[4-6]

Çocuk Diş Hekimliği günümüzde diş hekimliğinin en fazla gelişime açık olan ve en çok ihtiyaç duyulan diş hekimliği uzmanlık dallarının başında gelmektedir.[7] Bu gelişen uzmanlık dalı, diş hekimliğinin neredeyse tüm konularını ele almaktadır. Diğer bir yandan iletişim beceresi yüksek, sosyal yönü gelişmiş hekimlerin yetişmesine katkı sağlamaktadır. Tüm bu sebeplerden dolayı yeni mezun hekimler arasında popülaritesi artmış ve en çok tercih edilen uzmanlık dallarından biri haline gelmiştir.[8]

Türkiye'de Pedodonti alanında lisansüstü eğitim almak isteyen diş hekimleri ya doktora eğitim programına başvurarak ya da Diş Hekimliğinde Uzmanlık Sınavı'nı (DUS) kazanarak lisansüstü eğitim alabilmektedir. Çocuk Diş Hekimliği uzmanlık eğitimi, fakülte eğitimden sonra üç yıllık lisansüstü eğitimini kapsayan bir süreçtir. Bu eğitimin en önemli parçalarından birisi de tez yazmaktır. Hem uzmanlık hem de doktora eğitiminin tamamlanabilmesi için tezin yasal olarak başarılı olması zorunluluğu vardır.[9]

Uzmanlık ve doktora tezleri, bilimsel araştırmanın ilk basamağıdır. Tez yazma süreci uzmanlık ve doktora öğrencilerine önemli beceriler kazandırmaktadır. Bu becerilerin başında hipotez oluşturma, veri toplama, verileri analiz etme ve sonuçları değerlendirme gelmektedir.[7]

Literatüre bakıldığında ülkemizde diş hekimliğinde lisansüstü eğitimde tamamlanan tezlerin incelenmesine yönelik sınırlı sayıda çalışma yapılmıştır. Meriç ve ark. yaptıkları çalışmada 2017-2021 yılları arasında Ortodonti lisansüstü eğitiminde hazırlanan tezleri incelemişlerdir.[10] Özkalaycı ve ark. ise yaptıkları çalışmada 2016-2020 yılları arasında Ortodonti lisansüstü eğitiminde hazırlanan tezlerin yayınlanma oranlarını incelemişlerdir.[11] Yurtdışı literatüre bakıldığında, Garcia ve ark. 2008-2020 yılları arasında Pedodonti dergilerinde yayınlanan makalelerin bibliyometrik analizini yaparak makale ve yazar bazlı parametreleri incelemişlerdir.[12] Bununla birlikte, Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminde tamamlanan tezler ile ilgili yapılan herhangi bir çalışma bulunmamaktadır. Bu çalışmada; Türkiye'de Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminde tamamlanan tezleri incelemek ve belirlenen kriterler doğrultusunda değerlendirmek amaçlanmıştır.

GEREÇ VE YÖNTEM

Bu çalışmada, yalnızca Türkiye Ulusal Tez Merkezi'nin (www.tez.yok.gov.tr) 30 Mayıs 2023 tarihli herkesin erişimine açık olan tezler değerlendirilmiştir ve hiçbir katılımcı çalışmaya dâhil edilmemiştir.

Çalışma için Türkiye'de Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitimde tamamlanan doktora ve uzmanlık tezleri incelenmiştir. Çalışmaya dahil edilecek tezlerin belirlenebilmesi için arama motorunun detaylı tarama kısmında bir arama yapılmıştır. Arama anabilim dalına göre filtrelenmiş ve sadece Pedodonti (Çocuk Diş Hekimliği) alanındaki doktora ve uzmanlık tezleri taranmıştır.

Tezlerin çalışmaya dahil edilme kriterleri şu şekilde belirlenmiştir:

Türkiye'deki devlet veya vakıf/özel üniversitelerde yürütülmüş ve tamamlanmış olan Pedodonti (Çocuk Diş Hekimliği) alanındaki doktora veya uzmanlık tezleri,

Ulusal Tez Merkezi'ne yüklenmiş ve 2012-2022 yılları arasında tamamlanmış olan doktora veya uzmanlık tezleridir.

Tezlerin çalışmadan hariç tutulma kriterleri şu şekilde belirlenmiştir:

Ulusal Tez Merkezi'ne yüklenmemiş veya henüz tamamlanmamış tezler, Yüksek lisans tezleri, 2012-2022 yılları arasında olmayan veya Pedodonti (Çocuk Diş Hekimliği) alanının dışındaki tezlerdir.

Çalışmaya dahil edilen tezler yıl, üniversitenin adı, üniversitenin devlet veya vakıf/özel oluşu, üniversitenin bulunduğu coğrafi bölge, tez türü (doktora veya uzmanlık), yazarın cinsiyeti, danışmanın unvanı,danışmanın cinsiyeti, konu, metodoloji ve amaç başlıkları altında değerlendirilmiştir. Veriler IBM SPSS V23. paket programı kullanılarak istatistiksel olarak analiz edilmiştir. Kategorik veriler frekans (yüzde) olarak hesaplanmıştır.

BULGULAR

2012-2022 yılları arasında 293 doktora ve 446 uzmanlık tezi olmak üzere toplam 739 tez olduğu tespit edilmiştir. En fazla tez 2022 yılında (133 tez, %18) ve en az tez 2012 yılında (32 tez, %4.3) tamamlanmıştır. Tezlerin yıllara göre dağılımları Tablo 1'de sunulmuştur.

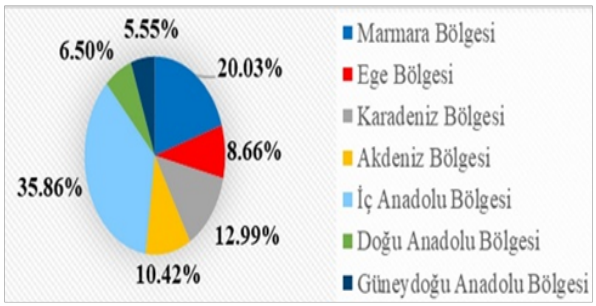
Tezlerin yürütüldüğü üniversitelere göre dağılımları incelendiğinde, toplam 39 üniversitenin tez kayıtlarına ulaşılmıştır. En fazla tez tamamlayan üniversitenin devlet üniversiteleri arasında Marmara Üniversitesi (54 tez, %7.3) ve vakıf/özel üniversiteler arasında ise Yeditepe Üniversitesi (26 tez, %3.5) olduğu tespit edilmiştir (Tablo 2). Üniversitelerin devlet veya vakıf/özel oluşu incelendiğinde, 700 tezin (%94.7) devlet üniversitesinde ve 39 tezin (%5.3) vakıf/özel üniversitede tamamlanmış olduğu görülmüştür. Tezlerin coğrafi bölgelerimize göre dağılımları incelendiğinde, en çok İç Anadolu Bölgesi'nde (265 tez,%35.9) ve en az Güneydoğu Anadolu Bölgesi'nde (41 tez, %5.6) tezlerin tamamlandığı görülmüştür (Şekil 1).

Tablo 1. Tezlerin yıllara göre dağılımları

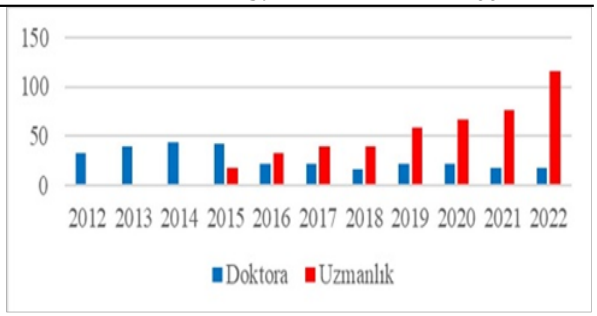
Yıl	Tez Sayısı	Yüzde (%)
2012	32	4.33
2013	39	5.28
2014	44	5.95
2015	60	8.12
2016	53	7.17
2017	62	8.39
2018	55	7.44
2019	79	10.69
2020	89	12.04
2021	93	12.58
2022	133	18.0
Toplam	**739**	**100**

Tablo 2. Tezlerin üniversitelere göre dağılımı

Üniversite	Tez Sayısı	Yüzde (%)
Marmara	54	7.31
Gazi	47	6.36
Ankara	45	6.09
İstanbul	44	5.95
Selçuk	38	5.14
Hacettepe	36	4.87
Süleyman Demirel	32	4.33
Dicle, Ondokuz Mayıs	30	4.06
Atatürk, Ege	29	3.92
Karadeniz Teknik	27	3.65
Yeditepe	26	3.52
Sivas Cumhuriyet	22	2.98
Erciyes	21	2.84
Kırıkkale	20	2.71
İnönü	19	2.57
Çukurova	18	2.44
Akdeniz	17	2.30
Eskişehir Osmangazi, Necmettin Erbakan, Ordu	14	1.89
İzmir Katip Çelebi	12	1.62
Bülent Ecevit, Gaziantep	11	1.49
Aydın Adnan Menderes, Bezmi Alem, Hatay Mustafa Kemal	10	1.35
Recep Tayyip Erdoğan	8	1.08
Kocaeli, Sağlık Bilimleri	7	0.95
Tokat Gaziosmanpaşa	6	0.81
Uşak	5	0.68
Pamukkale, Afyonkarahisar	4	0.54
Trakya	3	0.41
Başkent, GATA	2	0.27
Medipol	1	0.14
Toplam	**739**	**100**



Şekil 1: Tezlerin bölgelere göre dağılımları



Şekil 2: Tez türlerinin yıllara göre dağılımları

Tezlerin türlerine göre dağılımları incelendiğinde, 293'ünün doktora (%39.6) ve 446'sının uzmanlık (% 60.4) tezi olduğu görülmüştür. Ülkemizde uzmanlık eğitimin başlamasını takiben doktora tezlerinde azalma ve uzmanlık tezlerinde artış olduğu tespit edilmiştir. Tez türlerinin yıllara göre dağılımları Şekil 2'de sunulmuştur.

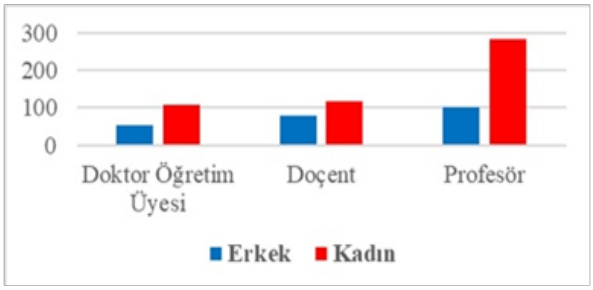
Tezlerin yazarın cinsiyetine göre dağılımları incelendiğinde, 636 tez (%86.1) kadın yazarlar tarafından yazılırken,103 tez (%13.9) erkek yazarlar tarafından yazılmıştır.

Tezlerin danışman unvanına göre dağılımları incelendiğinde,160'ının doktor öğretim üyesi (%21.6), 194'ünün doçent (%26.3) ve 385'inin profesör (%52.1) bir danış-

man tarafından yürütüldüğü tespit edilmiştir. Eş danışman varlığı incelendiğinde, 47 tezin (%6.4) eş danışmanı varken 692 tezin (%93.6) eş danışmanının olmadığı görülmüştür. Danışman cinsiyetine göre dağılım incelendiğinde, 507'sinin kadın (%69.9) ve 232'sinin erkek danışman (%30.1) olduğu görülmüştür. Şekil 3'te danışmanların unvan ve cinsiyete göre dağılımları sunulmuştur.

Tezlerin konusuna göre dağılımları incelendiğinde, tezlerin en çok çürük/koruyucu, restoratif ve protetik uygulamalar (306 tez, %41.4) ve en az ise yapay zeka/stres analizi/sonlu elemanlar (11 tez, %1.5) ve dudak damak yarığı/buruksizm/temporomandibular eklem rahatsızlığı (12 tez, %1.6) konu başlıkları altında toplandığı tespit edilmiştir (Tablo 3).

Tezlerin metodolojilerine göre dağılımları incelendiğinde, laboratuvar çalışması/in vitronun en çok kullanılan (286 tez, %38.7) ve bilgisayar tabanlı çalışma/in silikonun (12 tez, %1.6) en az kullanılan metodoloji olduğu görülmüştür (Tablo 4).



Şekil 3: Danışmanların unvan ve cinsiyete göre dağılımları

Tezlerin amaçlarına göre dağılımları incelendiğinde en çok malzeme başarısı (çekme, kırma vb. deneysel) (284 tez,%38.4) ve tanısal, geçerlilik, güvenilirlik (221 tez, % 29.9), en az ise yapay zeka/stres analizi/gerilme analizi (11 tez,%1.5) başlığında tezlerin yürütüldüğü tespit edilmiştir (Tablo 5).

TARTIŞMA

Tez bilimsel bir araştırmanın raporlandığı ve araştırmacının somut bir konu üzerinde sistematik ve tarafsız bir araştırma sonucunda elde ettiği bulguları teorik bir altyapıya sahip olarak derlediği bilimsel çalışmadır.[13]Aynı zamanda uzmanlık ve doktora eğitimlerinin önemli bir parçasıdır.[9] Lisansüstü eğitimin bu önemli parçasındaki eğilimlerin analizi hem ülkemiz Pedodonti (Çocuk Diş Hekimliği) akademik yaklaşımının değerlendirilmesini sağlayacak, hem de yazarlara yapmayı düşündükleri tez ve makale çalışmalarını belirlerken önemli bir rehber olacaktır.

Bu çalışma için literatürü incelediğimizde, konuyla ilgili Pedodonti (Çocuk Diş Hekimliği) alanında yapılmış bir çalışmanın olmadığı tespit edilmiştir. Bu konuya benzer bibliyometrik çalışmalara bakıldığında, çalışmaların popüler Pedodonti (Çocuk Diş Hekimliği) dergilerinde yayınlanan makaleleri inceleyip konu, çalışma tasarımı veya en çok atıfta bulunulan makaleler gibi parametrelerde incelemeler yaptıkları tespit edilmiştir.[12,14] Çalışmamızda ise tüm tezler daha detaylı parametreler dikkate alınarak değerlendirilmiştir. Ülkemizde Diş Hekimliğinde Uzmanlık Sınavı (DUS) başlangıç zamanı 2012 yılı olduğundan dolayı, geçmişten günümüze uzmanlık ve doktora eğitim programlarının karşılaştırılmasının yapılabilmesi için 2012-2022 yılları arasında tamamla-

Tablo 3. Tezlerin konusuna göre dağılımları

Konu	Tez Sayısı	Yüzde (%)
Çürük/ Koruyucu, Restoratif ve Protetik Uygulamalar	306	41.41
Endodontik Uygulamalar	96	12.99
Dudak Damak Yarığı/ Bruksizm/ Temporomandibular Eklem Rahatsızlığı	12	1.62
Radyoloji/ Sistemik Hastalıklar/ Dental Anomaliler	111	15.02
Oral Hijyen/ Ağız-Diş Sağlığı/ Periodontoloji/ Oral Mikrobiyom	44	5.95
Davranış Yönlendirme/Genel Anestezi	14	1.89
Yapay Zeka/Stres Analizi/Sonlu Elemanlar	11	1.49
Travma	22	2.98
Diğer (Birden Fazla Konu İçeren Tezler)	123	16.64
Toplam	**739**	**100**

Tablo 4. Tezlerin metodolojilerine göre dağılımı

Metodoloji	Tez Sayısı	Yüzde (%)
Klinik Çalışma/İn Vivo	111	15.02
Laboratuvar Çalışması/İn vitro	286	38.70
Ölçüm Çalışması (Model, Radyografi, Fotoğraf)	40	5.41
Deney Hayvanı Çalışması	17	2.30
Bilgisayar Tabanlı Çalışma/İn Siliko	12	1.62
Anket Çalışması	47	6.36
Diğer (Birden Fazla Yöntem İçerenler)	226	30.58
Toplam	**739**	**100**

Tablo 5. Tezlerin amaçlarına göre dağılımı

Amaç	Tez Sayısı	Yüzde (%)
Tedavi/Takip	119	16.10
Tanısal, Geçerlilik, Güvenilirlik	221	29.91
Malzeme Başarısı (Çekme, Kırma vb. Deneysel)	284	38.43
Yapay Zeka/Stres Analizi/Gerilme Analizi	11	1.49
Eğitim, Farkındalık, Bilgi, Memnuniyet	38	5.14
Diğer (Birden Fazla Amaç İçerenler)	66	8.93
Toplam	**739**	**100**

nan tez çalışmaları çalışmaya dahil edilmiştir.

Küçükeşmen ve ark. diş hekimliği lisans öğrencilerinde yaptıkları bir anket çalışmasında, öğrencilerin % 82.3'ünün uzmanlık ve doktora eğitiminin yapılması gerektiğini düşündüklerini bildirmişlerdir.[15] Özkalaycı ve ark. yaptıkları çalışmada ise uzmanlık eğitiminin doktora eğitimine göre daha fazla tercih edildiğini rapor etmişlerdir.[11] Çalışmamızda benzer olarak 2012 yılından 2022 yılına kadar olan tez sayılarında artış olduğu ve bu artışın doktora tezlerinin zaman içinde azalmasına rağmen uzmanlık tezlerinin ani artışından kaynaklandığı görülmüştür. Bu durumun uzmanlık eğitiminin 2012 yılından günümüze kadar popülerliğinin artması ve açılan yeni diş hekimliği fakültelerinin uzmanlık ve doktora programına dahil olmalarından dolayı artan kontenjan sayısından kaynaklandığı düşünülmektedir. Uzmanlık eğitiminin doktora eğitimine göre daha fazla tercih edilmesinin sebebinin ise uzmanlık eğitiminin hekime sağladığı statü ve ekonomik imkanlar olduğu düşünülmektedir.

Meriç ve ark. yaptıkları Ortodonti alanındaki çalışmada en fazla tezin tamamlandığı üniversitenin Süleyman Demirel Üniversitesi olduğunu rapor etmişlerdir.[10] Çalışmamızda ise tezlerin tamamlandığı üniversitelerin dağılımları incelendiğinde, Pedodonti (Çocuk Diş Hekimliği) alanında tüm üniversiteler arasında en fazla uzmanlık ve doktora tezi tamamlanan üniversitenin Marmara Üniversitesi olduğu görülmüştür. Bulgular arasındaki farklılık, incelenen tezlerin farklı uzmanlık alanlarında olmasından veya üniversitelerin akademik kadro ve eğitim programları arasındaki farklılıklardan kaynaklanmış olabilir.

Kızılcı ve ark. diş hekimliği lisans öğrencilerinde yaptıkları bir anket çalışmasında kadınların Pedodonti uzmanlık eğitimini erkeklerden daha çok tercih ettiğini bildirmişlerdir.[16] Çalışmamızda da benzer olarak yazar ve danışman cinsiyeti incelendiğinde, kadın yazarların ve kadın danışmanların sayısı erkek yazar ve erkek danışmanların sayısına göre daha fazla olduğu görülmüştür. Bu bulgular ışığında Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminin kadınlar arasında daha popüler olduğu söylenebilir.

Ohta ve ark. bir Pedodonti dergisinin 20 yıllık bibliyometrik analizini yaptıkları çalışmada en çok tercih edilen konunun çürük olduğunu sonrasında ise restoratif diş hekimliğinin geldiğini bildirmişlerdir.[17] Benzer şekilde Poletto ve ark. bir Pedodonti dergisi üzerinde yaptıkları bibliyometrik çalışmada yayınlanan makalelerin konu dağılımları incelendiğinde, en çok tercih edilen konu başlığının çürük/koruyucu diş hekimliği olduğunu, en çok tercih edilen ikinci konu başlığının ise restoratif diş hekimliği/dental materyaller olduğunu rapor etmişlerdir.[18] Çalışmamızda da tezlerin konu dağılımları incelendiğinde benzer şekilde sonuçlar ile karşılaşılmıştır. Tez konusu seçiminin en fazla çürük/koruyucu, restoratif ve protetik uygulamalar ile ilgili olduğu görülmüştür. Türkiye Ağız ve Diş Sağlığı Profili 2018 (TADSAP-2018) verilerine göre; beş yaş grubunda çürük prevalansı %64.4'tür ve her on çocuktan yaklaşık yedisi daha önce bir diş hekimine gitmemiştir. On iki yaş grubunda ise çürük prevalansı % 46.6'dır ve her dört çocuktan biri daha önce bir diş hekimine gitmemiştir. Tespit edilen veriler dikkate alındığında ülkemizde çürük prevalansı yüksektir ve diş hekimine gitme oranı ise oldukça düşüktür. Ülkemizde çürük oranının bu denli yüksek olmasının tez konularında da bu konuya eğilimin artmasına katkı sağladığı söylenebilir.[19]

Meriç ve ark. yaptıkları çalışmada tezlerin metodolojisine göre inceleme yapıldığında Ortodonti alanında daha çok klinik çalışma/in vivo'nun yapıldığını rapor etmişlerdir.[10] Bununla birlikte çalışmamızda Pedodonti (Çocuk Diş Hekimliği) alanında tamamlanan tezlerin metodolojisi incelendiğinde, laboratuvar çalışması/in vitronun daha çok tercih edildiği görülmüştür. Bu durum uzmanlık alanlarındaki klinik çalışma farklılığı, klinik çalışmaların uzun sürmesi, etik kaygılar, Çocuk Diş Hekimliği uzmanlık eğitiminin diğer bazı branşlara göre uzmanlık eğitim süresinin daha kısa fakat rotasyon eğitimlerinin daha fazla oluşu ile açıklanabilir.

Çalışmamızda en az tercih edilen metodoloji bilgisayar tabanlı çalışma/in siliko olmuştur. Bununla birlikte, yapılan pek çok çalışmada bilgisayar tabanlı çalışmaların teknolojinin gelişimiyle birlikte ilerleyen yıllarda artacağı bildirilmiştir.[20–24] Benzer şekilde teknolojik gelişmeler ile paralel olarak, ilerleyen yıllarda yapay zeka, sonlu elemanlar analizi, üç boyutlu yazıcılar ve üç boyutlu görüntüleme yöntemleri gibi konularda popülerliğin artması beklenmektedir.

Bu çalışmanın bazı sınırlılıkları vardır. İlk olarak bu çalışmada 2012-2022 yılları arasındaki tezler değerlendirilmiştir. Farklı zaman dilimlerinde bulgularda değişiklik olabilir. İkinci olarak bu çalışmada ülkemizde Pedodonti (Çocuk Diş Hekimliği) alanındaki tezler değerlendirilmiştir. Farklı alanlarda bulgularda değişiklik olabilir. Son olarak bu çalışmada tamamlanmış ve Ulusal Tez Merkezi'ne yüklenmiş tezler değerlendirilmiştir. Bununla birlikte, henüz tamamlanmamış veya tamamlandığı halde Ulusal Tez Merkezi'ne yüklenmemiş tezler bulunabilir. Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitiminde tamamlanan tezlerin araştırma alanındaki eğilimleri anlayabilmek için daha ileri çalışmalar yapılması gerekmektedir.

SONUÇ

Çalışmamızın sınırları dahilinde aşağıdaki sonuçlar elde edilmiştir:

Ülkemizde uzmanlık eğitimin başlamasını takiben doktora tezlerinin sayısı azalırken uzmanlık tezlerinin sayısında artış görülmüştür.

Ülkemizde Pedodonti (Çocuk Diş Hekimliği) lisansüstü eğitimi kadınlar arasında daha popülerdir.

Tezler en çok çürük/koruyucu, restoratif ve protetik uygulamalar (306 tez, %41.4) ve en az ise yapay zeka/ stres analizi/sonlu elemanlar (11 tez, %1.5) ve dudak damak yarığı/buruksizm/temporomandibular eklem rahatsızlığı (12 tez, %1.6) konusundadır.

Etik Komite Onayı: Bu çalışmada, yalnızca Türkiye Ulusal Tez Merkezi'nin (www.tez.yok.gov.tr) 30 Mayıs 2023 tarihli, herkesin erişimine açık olan tezler değerlendirilmiştir. Bu yüzden etik kurul onayına ihtiyaç duyulmamıştır.

Bilgilendirilmiş Onam: Çalışmada, hiçbir katılımcı dâhil edilmemiştir. Bu yüzden bilgilendirilmiş onam yer almamaktadır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Konsept - ÇG; Tasarım - ÇG; Denetim -

ÇG; Veri Toplama ve/veya İşleme - ESA; Analiz ve/veya Yorum - ÇG; Literatür Taraması - ESA; Yazma - ÇG, ESA; Eleştirel İnceleme - ÇG.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

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Ethics Committe Approval: In this study, only publicly accessible theses dated May 30, 2023 of the Türkiye National Thesis Center (www.tez.yok.gov.tr) were evaluated. There fore, ethics committee approval was not required.

Informed Consent: No participants were included in the study. There fore, informed consent is not included.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - CG; Design - CG; Supervision - CG; Data Collection and/or Processing - ESA; Analysis and/or Interpretation - CG; Literature Search - ESA; Writing Manuscript - CG, ESA; Critical Review - CG.

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GIDA KATKI MADDELERİ HAKKINDA BİR BİLGİLENDİRME KAYNAĞI OLARAK YOUTUBE VİDEOLARININ DEĞERLENDİRİLMESİ

ASSESSMENT OF YOUTUBE VIDEOS AS A SOURCE OF INFORMATION ABOUT FOOD ADDITIVES

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ÖZ

Nüfusun artması ve yemek kültürünün değişmesi ile gıda katkı maddelerinin sayısı ve çeşidi önemli ölçüde artmıştır. Gıda katkı maddelerinin kontrolsüz ve amaçları dışında kullanımını önlemek için çeşitli yasal düzenlemeler olsa da tüketiciler arasında gıda katkı maddelerinin zararlı olduğuna dair yanlış bir inanç vardır. Ayrıca son yıllarda insanlar sağlık bilgilerine erişmek için interneti daha fazla kullanmaya başlamıştır. YouTube™, beslenme ve sağlık bilgilerine erişmek için sıklıkla kullanılan platformlardan biridir. Ancak paylaşılan bilgiler için ne yazık ki bir denetim mekanizması bulunmamaktadır. Ayrıca gıda katkı maddeleri gibi tartışmalı konularda ortaya çıkan bilgi kirliliği, bu denetimin önemini daha da artırmaktadır. Bu nedenle, bu çalışmanın amacı, gıda katkı maddeleri hakkında bir bilgilendirme kaynağı olarak YouTube videolarını değerlendirmektir. Çalışmaya 96 video dahil edilmiştir. Videonun ismi, linki, yüklenme tarihi, süresi, görüntülenme sayısı, yorum sayısı, beğenme ve beğenmeme sayısı ve yükleme kaynağı bilgileri (Kişisel bloglar, sağlık profesyonelleri ve gıda profesyonelleri) kaydedilmiştir. Daha sonra izlenme oranı, beğenme oranı ve video güç indeksi (Video Power Index-VPI) değerleri hesaplanmıştır. Video kalitesini değerlendirmek için araştırmacılar tarafından oluşturulan İçerik Değerlendirme Skoru, Modifiye DISCERN Ölçeği ve Global Kalite Skoru (Global Quality Score-GQS) kullanılmıştır. Videolar, gıda katkı maddeleri konusunda bilgi sahibi iki araştırmacı tarafından izlenerek değerlendirilmiştir. Çalışmanın temel bulguları, gıda profesyonelleri tarafından paylaşılan videoların GQS ve İçerik Değerlendirme Skorunda sağlık profesyonelleri ve kişisel bloglardan daha yüksek puan aldığını ortaya koymuştur ($p<0.001$). Her üç ölçekte en düşük puan alan videolar kişisel bloglar tarafından paylaşılanlar olmuştur ($p<0.001$). Ayrıca İçerik Değerlendirme Skoru ile VPI ($r=0.308$, $p=0.002$) ve izlenme oranları ($r=0.308$, $p=0.002$) arasında pozitif korelasyon olduğu belirlenmiştir. Ancak video kalitesi puanları ile beğenme oranlarının negatif ilişkili olduğu saptanmıştır ($p<0.05$). Sonuçlar, gıda katkı maddeleri konusunda uzmanlar tarafından yapılan bilgilendirmenin önemini göstermiş olup, YouTube™ platformunda beslenme ve sağlık alanında yayımlanan videoların denetlenmesinin önemini vurgulamıştır.

Anahtar kelimeler: Bilgi kaynağı, gıda katkı maddeleri, video, YouTube

ABSTRACT

With the increase in population and change in food culture, the number and variety of food additives have increased significantly. Although there are various legal regulations to prevent the uncontrolled and unintended use of food additives, there is a false belief among consumers that food additives are harmful. Additionally, in recent years, people have begun to use the internet more to access health information. YouTube™ is a frequently used platform to access nutrition and health information. However, unfortunately, there is no control mechanism for the information shared. In addition, the information pollution that arises on controversial issues such as food additives further increases the importance of this control. Therefore, the aim of this study was to evaluate YouTube videos as a source of information about food additives. Ninety-six videos were included in the study. The name of the video, its link, upload date, duration, number of views, comments, likes, and dislikes, and upload source information (Personal blogs, health professionals, and food professionals) were recorded. Then, viewing rates, like rates and video power index (VPI) values, were calculated. The Content Evaluation Score, created by the researchers, the Modified DISCERN Scale, and the Global Quality Score (GQS) were used to evaluate video quality. The videos were watched and evaluated by two researchers who are knowledgeable about food additives. The study's key findings revealed that videos shared by food professionals scored higher on the GQS and Content Evaluation Score than health professionals and personal blogs ($p<0.001$). The videos with the lowest scores on all three scales were those shared by personal blogs ($p<0.001$). Additionally, it was determined that there was a positive correlation between Content Evaluation Score and VPI ($r=0.308$, $p=0.002$) and viewing rates ($r=0.308$, $p=0.002$). However, it was found that video quality scores and liking rates were negatively related ($p<0.05$). The results demonstrated the importance of information provided by experts on food additives and emphasized the importance of monitoring videos published on the YouTube™ platform in nutrition and health.

Keywords: Information source, food additives, video, YouTube

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GİRİŞ

Gıda katkı maddeleri, "normalde gıda olarak tüketilmeyen ve normal olarak gıdanın tipik bir bileşeni olarak kullanılmayan; üretim, hazırlama ve işleme aşamalarında teknolojik bir amaç için gıdalara kasıtlı olarak eklenen, besleyici değeri olmayan herhangi bir madde" olarak tanımlanmaktadır.[1] Türk Gıda Kodeksi Gıda Katkı Maddeleri Yönetmeliği'nde ise "tek başına gıda olarak tüketilmeyen, besleyici değeri olan veya olmayan, üretim, işleme gibi aşamalarda koruma, stabilize etme gibi teknolojik amaçlarla gıdaya ilave edilen, doğrudan ya da dolaylı olarak o gıdanın bileşeni haline gelen maddelere verilen genel ad" şeklinde tanımlanmıştır.[2] Gıda katkı maddeleri; gıdanın korunması ve raf ömrünün uzatılması, besin değerinin iyileştirilmesi, gıdanın renk, tat ve esneklik gibi belirli niteliklerinin geliştirmesi gibi birçok konuda yarar sağlamaktadır. Bu nedenle doğru kullanımı modern gıda endüstrisinde önemli bir rol oynamaktadır.[3]

Günümüzde toplum yapısının ve yemek kültürünün değişmesi, gıda katkı maddelerinin üretiminde, sayısında ve çeşidinde önemli bir artışa yol açmıştır. Bu durum, gıda katkı maddelerinin kontrolsüz ve amaçları dışında kullanımını önlemek için yasal düzenlemelerin yapılmasını gerektirmiştir.[4] Avrupa Birliği'nde (AB) bu konuda yetkilendirilmiş kuruluş Avrupa Gıda Güvenliği Kurumu (The European Food Safety Authority-EFSA)'dır.[5] Uluslararası bağlamda gıda katkı maddelerinin güvenilirliğinden sorumlu kuruluş, Gıda ve Tarım Örgütü (Food and Agriculture Organization-FAO) ve Dünya Sağlık Örgütü'nün (World Health Organization-WHO) birlikte oluşturduğu Birleşik Gıda Katkıları Uzman Komitesi'dir (Joint FAO/WHO Expert Committee on Food Additives-JECFA).[1] Türkiye'de ise bu görev Tarım ve Orman Bakanlığı'na verilmiştir. Ayrıca Türk Gıda Kodeksi'nin Gümrük Birliği uyarınca AB mevzuatı ile uyumlu olması da zorunludur.[2]

Gıda katkı maddelerinin güvenliği açısından en geçerli toksikolojik kriterlerden biri Günlük Kabul Edilebilir Alım (Acceptable Daily Intake-ADI) değeridir. Bu değer, ilgili katkı maddesinin insan sağlığı için günlük zararsız dozunu göstermektedir ve "mg/kg vücut ağırlığı" olarak ifade edilmektedir. Avrupa Birliği'nde ADI değeri belirlenen, yani EFSA tarafından onaylanan ve kullanımına izin verilen gıda katkı maddelerine "Europe" kelimesinin baş harfi kullanılarak E-kodları verilmektedir. Bu E-kodları, gıda katkı maddelerine ayrıntılı incelemeler sonrasında verilir ve katkı maddesinin kullanımının güvenli olduğu anlamına gelmektedir. Bu kodların uluslararası geçerliliği de bulunmaktadır.[5] Ancak özellikle 2000'li yılların başında çeşitli medya kuruluşlarında sık sık yapılan tartışmaların da gösterdiği gibi, tüketicilerde gıda güvenliği konularında gıda endüstrisine karşı önemli bir güvensizlik vardır.[6] Tüketiciler arasında tüm gıda katkı maddelerinin zararlı olduğu, E-kodlu katkı maddelerinin kansere neden olduğu, gıda katkı maddelerinin sadece paketli gıdalarda bulunduğu, katkı maddesi olmayan gıdaların daha sağlıklı olduğuna dair yanlış bir algı da vardır.[7] Ayrıca ülkemizde yapılan bir çalışmada tüketicilerin gıda katkı maddeleri hakkında orta düzeyde bilgi sahibi oldukları, eğitim ve iletişim eksikliğinin gıda katkı maddeleri konusundaki farkındalıklarını olumsuz yönde etkilediği bildirilmiştir.[8] Bir başka çalışmada ise tüketicilerin gıda katkı maddeleri ile ilgili bilgileri çoğunlukla kitle iletişim araçlarından edindiği belirlenmiştir. Ayrıca tüketicilerin % 81.0'i gıda katkı maddelerinin sağlığa zararlı olduğunu düşündüklerini beyan etmiştir.[9] Bu durum, tüketicilerin gıda katkı maddeleri ve işlevleri konusunda eğitilmesi ve bilinçlendirilmesi gerektiğini göstermektedir.

Son yıllarda insanlar sağlık bilgilerine erişmek için kitle iletişim araçlarına ek olarak interneti de daha fazla kullanmaya başlamıştır.[10] Sıklıkla kullanılan platformlardan biri de YouTube™'dur (http://www.youtube.com). Tüm sosyal medya ve web sayfaları arasında YouTube™, aylık 2.5 milyar aktif kullanıcı, 122 milyondan fazla günlük kullanıcı, bugüne kadar paylaşılan beş milyardan fazla video ve günde beş milyardan fazla izlenme sayısı ile oldukça popüler bir platformdur.[11] YouTube™, kullanıcıların videoları ücretsiz olarak görüntülemesine, yüklemesine ve indirmesine, yükleme kaynakları ile diğer izleyicilerin kolayca iletişim kurmasına ve yorum yapmasına olanak sağlamaktadır. Ancak YouTube™ videolarının en büyük dezavantajı, sağlık alanında bu videoların kalitesini ve bilimsel doğruluğunu izleyecek bir hakemli değerlendirme sisteminin bulunmamasıdır. Bu nedenle iletilen bilginin kalitesinin değerlendirilmesi oldukça önemlidir.[12] Ancak yapılan literatür taramasında YouTube™ platformunda gıda katkı maddeleri konusunda paylaşılan bilgilendirme videolarını değerlendiren bir çalışmaya rastlanmamıştır. Bu nedenle, bu çalışmanın amacı, gıda katkı maddeleri hakkında bir bilgilendirme kaynağı olarak YouTube™ videolarını değerlendirmektir.

GEREÇ VE YÖNTEM

Verilerin Toplanması

Veri toplamaya başlamadan önce YouTube™ arama geçmişi silinmiş, arama tercihi "videoları alaka düzeyine göre sırala" olarak seçilmiş ve 12.12.2023 tarihinde arama çubuğuna "Gıda katkı maddeleri", "Besin katkı maddeleri", "Tatlandırıcılar", "Doğal tatlandırıcılar, "Yapay tatlandırıcılar", "Gıda koruyucuları", "Besin koruyucuları", "Aroma vericiler", "Aroma artırıcılar", "Kıvam vericiler", "Kıvam artırıcılar" ve "Renklendiriciler" anahtar kelimeleri yazılmıştır. Bu arama kelimeler ile başlangıçta 550 videoya ulaşılmıştır. Ancak (1) yinelenen, (2) alakasız, (3) dili Türkçe olmayan, (4) sesli anlatım olmayan, (5) gıdalarla ilgili olmayan veya ana konusu gıda katkı maddeleri olmayan videolar, (6) televizyon kesitleri (haberler, kadın programları), (7) reklamlar, (8) 30 dk'dan uzun ve 1 dk'dan kısa olan videolar ve (9) son 5 yıla ait olmayan videolar çalışmaya dahil edilmemiştir. Dışlama kriterlerinin uygulanmasının ardından geriye kalan 96 video içerik ve kalite açısından ayrıntılı bir şekilde analiz edilmiştir.

Videoların Değerlendirilmesi

Videonun ismi, linki, yüklenme tarihi, süresi, görüntülenme sayısı, yorum sayısı, beğenme ve beğenmeme sayısı ve yükleme kaynağı [1. Sağlık profesyoneli (doktor, diyetisyen, fizyoterapist ve hemşire), 2. Gıda profesyoneli (Gıda mühendisi ve gastronomi uzmanı), 3. Kişisel blog] bilgileri kaydedilmiştir. Bu bilgiler kullanılarak izlenme oranı, beğenme oranı ve video güç indeksi (Video Power Index-VPI) değerleri hesaplanmıştır.[13] Hesaplamalara ait formüller aşağıda özetlenmiştir:

İzlenme Oranı(%)= (Görüntülenme sayısı / Yüklenmeden bugüne geçen gün sayısı) x 100

Beğenme Oranı =[Beğenme sayısı /(Beğenme sayısı + Beğenmeme sayısı)] x 100

Video Güç İndeksi (VPI) Değeri =[(Beğenme oranı x İzlenme oranı) /100] hesaplanmıştır.

Videoların kalite analizi için beş soruluk modifiye DISCERN Ölçeği,[14] Global Kalite Ölçeği[10] ve araştırmacılar tarafından literatür bilgilerinden yararlanarak oluşturulan İçerik Değerlendirme Skoru[1,2,5] kullanılmıştır. Çalışmada kullanılan ölçekler ve İçerik Değerlendirme Skoru, Tablo 1'de verilmiştir.

Modifiye DISCERN Ölçeği, görsel medya ve bilginin değerlendirilmesi amacıyla kullanılan, 5 sorudan oluşan bir ölçektir. Bütün videolar modifiye DISCERN Ölçeği kullanılarak içerikte yer alan bilgilerin güvenilirliği açısından değerlendirilmiş ve 1 ile 5 arasında puan verilmiştir.[14]

Seçilen tüm videoların genel kalitesini değerlendirmek için Global Kalite Skoru (GQS) kullanılmıştır. Global Kalite Ölçeği'nde toplam puan 1 ile 5 arasında değişmektedir. 1-2 puan düşük video kalitesi, 3 puan orta video kalitesi, 4-5 puan ise yüksek video kalitesini göstermektedir.[10]

Araştırmacılar tarafından oluşturulan İçerik Değerlendirme Skoru, 7 sorudan oluşmaktadır. Belirtilen soruya ait doğru bilginin videoda yer alması durumunda "1 puan", bilginin videoda bulunmaması durumunda "0 puan", yanlış bilgi verilmesi durumunda ise "-1 puan" verilmiştir ve toplam puanı, -7 ile +7 puan arasında değişmiştir. İçerik Değerlendirme Skoru, daha önce benzer çalışmalarda olduğu gibi, literatür bilgileri ışığında oluşturulmuştur.[15,16] Değerlendiriciler tarafından verilen puanlar, değerlendiriciler arası güvenilirlik açısından değerlendirilmiştir. Ancak YouTube™ video kalitesine ilişkin standart oluşturulmadığından geçerlilik açısından değerlendirilme yapılmamıştır.[16]

Literatürdeki diğer çalışmalara benzer şekilde, her video gıda katkı maddeleri konusunda bilgi sahibi olan iki araştırmacı tarafından[10,17] (G.K. ve E.K.K.) ayrı ayrı izlenerek Modifiye DISCERN Ölçeği, İçerik Değerlendirme Skoru ve GQS puanları verilmiştir. Daha sonra puanların ortalaması alınarak videonun nihai puanı oluşturulmuştur.

İstatistiksel Analizler

Verilerin değerlendirilmesinde SPSS istatistik paket programı (versiyon 22.0, USA, IBM Corp., 2013) kullanılmıştır. İki değerlendirici arasındaki güvenilirliği belirlemek için sınıflar arası korelasyon katsayısı (ICC) hesaplanmıştır. Değerlendiriciler arası uyumu ölçmek amacıyla ise Cohen'in kappa katsayısı (κ) hesaplanmıştır.[10] Sayısal değişkenlerin normal dağılıma uygunluğu histogram, q-q grafikleri ve Kolmogorov-Smirnov testi ile değerlendirilmiştir. Tanımlayıcı istatistikler kategorik değişkenler için sayı (n) ve yüzde (%), sayısal değişkenler için ise ortanca, 25. ve 75. persentil (Q1-Q3) olarak verilmiştir. Grupların karşılaştırılmasında Kruskal Wallis Testi kullanılmıştır. Karşılaştırmalarda anlamlı fark çıkan değişkenlerin çoklu karşılaştırmaları için Tamhane's T2 Post-Hoc Testi kullanılmıştır. Sayısal değişkenlerin birbirleri ile ilişkisi ise Spearman korelasyon analizi ile incelenmiştir. Tüm istatistiksel analizlerde $p<0.05$ düzeyi anlamlı olarak kabul edilmiştir.

BULGULAR

Çalışmada, dahil edilme kriterlerine uyan 96 YouTube™ videosu analiz edilmiştir. YouTube™ videolarına ilişkin genel bilgiler Tablo 2'de özetlenmiştir. Gıda katkı maddeleri ile ilgili videolara en çok sırasıyla "Renklendiriciler" (%18.80) ve "Gıda katkı maddeleri" (%17.70) arama terimleri ile ulaşılmıştır. Videoların %40.60'ı kişisel blog sahipleri, %38.50'si sağlık profesyonelleri, %20.80'i ise gıda profesyonelleri tarafından yüklenmiştir. Video sürelerinin 233.50 (81.25-406.00) s olduğu, videoların yayımlandığı günden beri geçen gün sayısının 810.00 (203.50-1261.25) gün olduğu belirlenmiştir. Videoların görüntülenme sayısı 1122.00 (351.75-4608.00), beğenme sayısı 31.5 (9.00-135.50), beğenmeme sayısı 0.00 (0.00-2.00), yorum sayısı ise 3.00 (0.00-21.00)'tür. Videoların izlenme oranının 218.16 (57.53-1666.31), beğenme oranının 100.00 (98.70-100.00) olduğu saptanmıştır. Videoların VPI değeri 218.16

Tablo 1. Video kalitesini değerlendirmede kullanılan ölçekler

Tablo 1. Video kalitesini değerlendirmede kullanılan ölçekler

Modifiye DISCERN Ölçeği		
Sorular	**Evet**	**Hayır**
1. Videoda verilen bilgiler (hedefler) açık ve anlaşılır mı?		
2. Bilgi kaynakları güvenilir mi? (İddiaları desteklemek için alıntı yapılan geçerli çalışmalar, yayınlar vb.)		
3. Video sunulan bilgiler dengeli ve tarafsız mı?		
4. İzleyicinin yararlanabileceği öğrenmeye yönelik ek bilgi kaynakları veriliyor mu?		
5. Video tartışmalı veya belirsiz olan alanları değerlendiriyor mu?		

Global Kalite Skoru	
Derece	**Kalitenin Tanımı**
1	Kalitesiz ve hasta/izleyici eğitimi için kullanılma olasılığı düşüktür.
2	Bazı bilgiler mevcut olmadığı için kalitesiz ve hastalar/izleyiciler için sınırlı kullanımı var.
3	Yetersiz kalite ve akış; hastalar/izleyiciler için biraz yararlı, önemli konular eksik; bazı bilgiler mevcuttur.
4	İyi kalite ve akış; en önemli konular ele alındığı için hastalar/izleyiciler için yararlıdır.
5	Mükemmel kalite ve akış; hastalar/izleyiciler için son derece yararlıdır.

İçerik Değerlendirme Skoru			
No.	**İçerik**	**Evet**	**Bilgi yok**	**Hayır**
1	Gıda katkı maddelerinin/ilgili gıda katkı maddesinin tanımı doğru yapılmış mı?			
2	E kodlarının tanıtımı-açıklaması doğru yapılmış mı?			
3	İlgili gıda katkı maddesinin E kodu doğru verilmiş mi?			
4	Gıda katkı maddelerinin/ilgili gıda katkı maddesinin kullanım amacı doğru belirtilmiş mi?			
5	Gıda katkı maddelerinin/ilgili gıda katkı maddesinin kabul edilebilir günlük alım miktarı (ADI) doğru belirtilmiş mi?			
6	Gıda, katkı maddelerinin/ilgili gıda katkı maddesinin bulunduğu besinler hakkında doğru bilgi veriyor mu?			
7	Gıda katkı maddelerinin/ilgili gıda katkı maddesinin bulunmasının yasak olduğu besinler hakkında doğru bilgi veriyor mu?			

(57.53-1639.51), DISCERN Ölçeği puanı 2.00 (1.50-3.00), GQS puanı 2.50 (1.50-3.00) iken, İçerik Değerlendirme Skoru 1.75 (1.00-2.50) bulunmuştur.

Yükleme kaynağına göre YouTube™ videolarına ilişkin bilgilerin karşılaştırılması Tablo 3'te verilmiştir. Gıda profesyonelleri ve sağlık profesyonelleri tarafından paylaşılan videoların Modifiye DISCERN Ölçeği puanlarının kişisel bloglardan anlamlı olarak daha yüksek olduğu saptanmıştır (p<0.001). İçerik Değerlendirme Skoru ve GQS puanlarının ise gıda profesyonelleri grubunda hem sağlık profesyonelleri hem de kişisel bloglardan anlamlı olarak daha yüksek olduğu belirlenmiştir (p<0.001).

Video kalitesi değerlendirme ölçeklerine verilen puanlara göre iki değerlendirici arasındaki güvenilirliğin değerlendirilmesinde ICC ve κ katsayısı kullanılmıştır. Buna göre her üç ölçek için de ICC değerine göre değerlendiricilerin oldukça güvenilir olduğu (ICC>0.60), κ katsayısı sonucuna göre ise önemli düzeyde uyum gösterdikleri (κ>0.60) belirlenmiştir (Tablo 4).

Tablo 5'te kullanılan ölçeklerin puanları arasındaki korelasyon verilmiştir. İçerik Değerlendirme Skoru, GQS

Tablo 2. YouTube™ videolarına ilişkin genel bilgiler

Parametreler	Sayı (n=96)	Yüzde (%)
Arama terimi		
Renklendiriciler	18	18.80
Gıda katkı maddeleri	17	17.70
Besin katkı maddeleri	15	15.60
Tatlandırıcılar	15	15.60
Doğal tatlandırıcılar	15	15.60
Gıda koruyucuları	8	8.30
Kıvam arttırıcılar	3	3.10
Aroma vericiler	3	3.10
Aroma arttırıcılar	2	2.10
Yükleme Kaynağı		
Kişisel blog	39	40.60
Sağlık profesyoneli	37	38.50
Gıda profesyoneli	20	20.80
	Ortanca (Q1-Q3)	
Video süresi (s)	233.50 (81.25-406.00)	
Yayımlandığı günden beri geçen gün sayısı	810.00 (203.50-1261.25)	
Görüntülenme sayısı	1122.00 (351.75-4608.00)	
Beğenme sayısı	31.5 (9.00-135.50)	
Beğenmeme sayısı	0.00 (0.00-2.00)	
Yorum sayısı	3.00 (0.00-21.00)	
Etkileşim indeksi	2.97 (1.51-5.01)	
İzlenme oranı	218.16 (57.53-1666.31)	
Beğenme oranı	100.00 (98.70-100.00)	
VPI	218.16 (57.53-1639.51)	
Modifiye DISCERN Ölçeği	2.00 (1.50-3.00)	
GQS	2.50 (1.50-3.00)	
İçerik Değerlendirme Skoru	1.75 (1.00-2.50)	

Kısaltmalar: GQS, Global Quality Scale (Global Kalite Skoru); s, saniye; VPI, Video Power Index (Video Güç İndeksi).Q1-Q3: 25. ve 75. Persentil

Tablo 3. Yükleme kaynağına göre YouTube™ videolarına ilişkin bilgilerin karşılaştırılması

Parametreler	Kişisel blog (n=39)	Sağlık profesyoneli (n=37)	Gıda profesyoneli (n=20)	p*
Video süresi (s)	195.00 (64.00-355.00)	251.00 (70.00-432.50)	250.00 (139.25-499.50)	0.509
Yayımlandığı günden beri geçen gün sayısı	819.00 (75.00-1346.00)	768.00 (198.50-1090.50)	863.00 (369.00-1412.00)	0.606
Görüntülenme sayısı	887.00 (298.00-3835.00)	745.00 (257.00-4623.50)	1557.50 (922.00-14676.25)	0.082
Beğenme sayısı	23.00 (7.00-84.00)	21.00 (8.00-181.00)	57.00 (12.75-288.25)	0.278
Beğenmeme sayısı	0.00 (0.00-2.00)	0.00 (0.00-2.00)	0.00 (0.00-6.75)	0.715
Yorum sayısı	3.00 (1.00-12.00)	2.00 (0.00-25.50)	5.50 (1.00-37.00)	0.570
İzlenme oranı	360.82 (37.93-1976.47)	127.11 (48.99-622.75)	686.39 (96.32-2283.40)	0.178
Beğenme oranı	100.00 (98.88-100.00)	100.00 (98.45-100.00)	100.00 (98.43-100.00)	0.827
VPI	356.77 (37.93-1976.47)	123.65 (49.00-617.63)	661.12 (96.32-2283.40)	0.176
Modifiye DISCERN Ölçeği	1.50 (1.00-2.00)[a]	2.50 (1.75-3.00)[b]	3.00 (2.00-4.00)[b]	**<0.001**
GQS	2.00 (1.50-2.50)[a]	2.50 (2.00-3.00)[a]	3.75 (3.00-4.00)[b]	**<0.001**
İçerik Değerlendirme Skoru	1.50 (1.00-2.00)[a]	1.50 (0.75-2.00)[a]	4.00 (2.00-4.00)[b]	**<0.001**

Kısaltmalar: GQS, Global Quality Scale (Global Kalite Skoru); s, saniye; VPI, Video Power Index (Video Güç İndeksi).
*Kruskal Wallis Testi ve ardından Tamhane T2 post-hoc testi kullanılmıştır. Veriler, ortanca (Q1-Q3) olarak verilmiştir. (Q1-Q3: 25. ve 75. persentil) Farklı üs harflerine sahip parametreler (a, b, c) birbirinden anlamlı olarak farklıdır, p<0.05.

Tablo 4. Video kalitesi değerlendirme ölçeklerine verilen puanlara göre değerlendiriciler arası güvenilirliğin değerlendirilmesi

Parametreler	Modifiye DISCERN Ölçeği	GQS	İçerik Değerlendirme Skoru
ICC	0.863	0.929	0.941
κ	0.611	0.631	0.613

Kısaltmalar: GQS, Global Quality Scale (Global Kalite Skoru); ICC, Interclass Correlation Coefficient (Sınıflar Arası Korelasyon Katsayısı); κ, Cohen'in kappa katsayısı.

ile yüksek düzeyde anlamlı pozitif korelasyon (r=0.799, p<0.001), Modifiye DISCERN Ölçeği ile zayıf düzeyde anlamlı pozitif korelasyon (r=0.384, p<0.001) göstermiştir. Modifiye DISCERN Ölçeği ile GQS arasında ise orta düzeyde anlamlı pozitif korelasyon (r=0.691, p<0.001) gözlemlenmiştir.

ayrıntılı bir analizi sunulmuştur. Çalışmanın temel bulguları, gıda profesyonelleri tarafından paylaşılan videoların video kalitesi değerlendirme araçlarından GQS ve İçerik Değerlendirme Skorunda sağlık profesyonelleri ve kişisel bloglardan daha yüksek puan aldığını ortaya koymuştur (Tablo 3). Her üç ölçek için de en düşük pu-

Tablo 5. Modifiye DISCERN Ölçeği, Global Kalite Skoru ve İçerik Değerlendirme Skoru puanları arasındaki ilişki

	Parametreler		
Parametreler*	**Modifiye DISCERN Ölçeği**	**GQS**	**İçerik Değerlendirme Skoru**
Modifiye DISCERN Ölçeği	-	**r=0.691** **p<0.001**	**r=0.384** **p<0.001**
GQS	**r=0.691** **p<0.001**	-	**r=0.799** **p<0.001**
İçerik Değerlendirme Skoru	**r=0.384** **p<0.001**	**r=0.799** **p<0.001**	-

Kısaltmalar: GQS, Global Quality Scale (Global Kalite Skoru). *Spearman Korelasyonu, p<0.05.

Tablo 6'da videoların kalitesi ile ilişkili parametreler özetlenmiştir. İzlenme oranı ile İçerik Değerlendirme Skoru arasında anlamlı pozitif korelasyon (r=0.308, p=0.002), beğenme oranı ile her üç ölçek puanları arasında anlamlı negatif korelasyon olduğu belirlenmiştir (p<0.05). Ayrıca VPI ile İçerik Değerlendirme Skoru arasında anlamlı pozitif korelasyon (r=0.308, p=0.002) olduğu saptanmıştır.

an alan videolar kişisel bloglar tarafından paylaşılanlar olmuştur. Sonuçlar, gıda katkı maddeleri konusunda uzmanlar tarafından yapılan bilgilendirmenin önemini bir kez daha göstermiş olup, YouTube™ platformunda beslenme ve sağlık alanında yayımlanan videoların içeriğini incelemenin önemini vurgulamıştır.

İnternet çağında bilgiye ulaşmak oldukça kolaylaşmıştır. Ancak güvenilir ve yeterli bilgiye ulaşmak zordur.[18] Bu

Tablo 6. Videoların kalitesi ile ilişkili parametreler

Parametreler*	Modifiye DISCERN Ölçeği	GQS	İçerik Değerlendirme Skoru
Etkileşim indeksi	r=-0.176 p=0.087	r=-0.151 p=0.141	r=0.147 p=0.154
İzlenme oranı	r=0.020 p=0.845	r=0.163 p=0.112	**r=0.308** **p=0.002**
Beğenme oranı	**r=-0.231** **p=0.024**	**r=-0.398** **p<0.001**	**r=-0.300** **p=0.003**
VPI	r=0.020 p=0.848	r=0.162 p=0.115	**r=0.308** **p= 0.002**

Kısaltmalar: GQS, Global Quality Scale (Global Kalite Skoru); VPI, Video Power Index (Video Güç İndeksi).
*Spearman Korelasyonu, p<0.05.

TARTIŞMA

Son yıllarda insanlar, beslenme ve sağlık bilgilerine erişmek için interneti daha fazla kullanmaya başlamışlardır. Buna paralel olarak YouTube™ platformunda yer alan beslenme ve sağlık temalı videoların sayısı ve izlenme oranlarının da artması muhtemeldir. Ancak bu platformda paylaşılan bilgilerin doğruluğunu değerlendirecek bir mekanizmanın bulunmaması yanlış bilginin yayılmasına neden olmaktadır. Bu durum, YouTube™ platformunda paylaşılan videoların kalite ve içerik açısından incelenmesini gerekli kılmaktadır. Bildiğimiz kadarıyla bu çalışma, YouTube™ platformunda gıda katkı maddelerine ilişkin mevcut bilgilerin değerlendirildiği ilk çalışmadır. Çalışmada, toplam süresi 10.9 saat ve izlenme sayısı yaklaşık 1 milyon olan 96 video değerlendirilmiş ve bilgi kaynağı olarak YouTube™ videolarının çalışmada analiz edilen 96 videonun yükleme kaynağı incelendiğinde %40.60'ının konunun uzmanı olmayan kişisel blog sahipleri tarafından paylaşıldığı görülmektedir. YouTube™ platformundaki bu kontrolsüz bilgi kirliliği, daha önce çeşitli çalışmalarda da gösterilmiştir.[19,20] Gıda katkı maddeleri gibi tartışmalı konularda bu bilgi kirliliği çok daha yanıltıcı olabileceğinden, tüketicilerin doğru kaynaklardan bilgiye ulaşmalarını sağlamak daha fazla önem kazanmaktadır.

Bu çalışmada videoların kalitesini ve içeriğini değerlendirmek amacıyla Modifiye DISCERN Ölçeği, GQS ve araştırmacılar tarafından oluşturulmuş İçerik Değerlendirme Skoru kullanılmıştır. Yükleme kaynağına göre GQS ve İçerik Değerlendirme skorları incelendiğinde, en yüksek puana gıda profesyonelleri tarafından yüklenen videoların sahip olduğu, sağlık profesyonelleri ve kişisel

bloglar tarafından yüklenen videoların ise benzer puana sahip oldukları belirlenmiştir. Modifiye DISCERN Ölçeğine göre ise gıda profesyonelleri ve sağlık profesyonelleri tarafından yüklenen videolar en yüksek puana sahip olurken, kişisel bloglar tarafından yüklenen videoların puanlarının en düşük olduğu görülmüştür (Tablo 3, p<0.001). Yapılan diğer çalışmalarda da konunun profesyonelleri tarafından yayımlanan videoların kalitesinin daha yüksek olduğu belirlenmiştir.[19,21,22] Gıda profesyonellerinin aldıkları eğitim ve çalışma alanları düşünüldüğünde en yüksek puanı almaları beklenen bir durumdur. Videoların içeriklerine bakıldığında gıda profesyonellerinin genel olarak Türk Gıda Kodeksi Gıda Katkı Maddeleri Yönetmeliği'ne uygun açıklamalar yaptığı, sağlık profesyonellerinin ise daha çok gıda katkı maddelerinin sağlık üzerine olumsuz etkileri konusunda bilimsel olarak doğruluğu kanıtlanmamış konularda bilgi verdiği görülmüştür. Ayrıca sağlık profesyonellerinin İçerik Değerlendirme Skoru ve GQS puanlarının kişisel blog sahiplerine benzer olması da gıda katkı maddeleri konusunda bilgi düzeylerinin artırılması gerektiğini düşündürmüştür.

Bu çalışmada videoların kalitesini değerlendirmek için kullanılan ölçeklerin puanları arasındaki korelasyon da incelenmiştir ve üç ölçeğin de birbiri ile pozitif korelasyon gösterdiği bulunmuştur (Tablo 5). Bu durum, araştırmacılar tarafından oluşturulmuş olan İçerik Değerlendirme Skoru'nin gıda katkı maddeleri ile ilgili videoların içeriğini değerlendirmede uygun olabileceğini düşündürmüştür. Ayrıca değerlendiricilerin ölçeklere verdikleri puanların ICC ve κ değerleri de yapılan değerlendirmenin güvenilir olduğunu göstermiştir (Tablo 4).

Mevcut çalışmanın bulguları, İçerik Değerlendirme Skoru ile VPI değerlerinin pozitif korelasyon gösterdiğini ortaya çıkarmıştır. Video güç indeksi, videoların popülerliğini belirlemede kullanılan bir araçtır.[23] Videoların yükleme kaynağına göre bir fark olmasa da İçerik Değerlendirme Skoru ile VPI arasında pozitif korelasyon olması, gıda katkı maddeleri konusunda içerik açısından daha kaliteli videoların daha popüler olduğu anlamına gelebilir. Ancak literatürde bu konu ile ilgili sonuçlar çelişkilidir.[24,25] Bu durum, video içerikleri ve izleyici kitlesinin farklılığından kaynaklanmış olabilir. Ayrıca mevcut çalışmada İçerik Değerlendirme Skoru ile izlenme oranı arasında da pozitif bir ilişki olduğu belirlenmiştir (Tablo 6). Bu sonuç, izleyicilerin çoğunlukla yüksek kaliteli videolar izlediğini gösteren diğer çalışmalar ile uyumludur.[24,26] Ancak video kalitesi puanları ile beğenme oranlarının negatif ilişkili olması izleyicilerin kaliteli videoları daha az beğendiklerine işaret etmektedir. Lee ve ark.[20] tarafından yapılan bir çalışmada ise izleyicilerin yanıltıcı videoları güvenilir videolardan daha fazla izleme eğiliminde oldukları rapor edilmiştir. Mevcut izleme oranı açısından tam tersi bir sonuca ulaşılsa da izleyicilerin güvenilir olmayan videoları daha fazla beğenme eğiliminde oldukları düşündürmüştür.

SONUÇ

Sonuç olarak, YouTube™ platformunda gıda katkı maddelerine ilişkin farklı yükleme kaynakları tarafından sunulan çok miktarda bilgi mevcut olsa da bu videoların bazılarının içerik ve kalite açısından uygun olmadığı saptanmıştır. Genel olarak gıda profesyonelleri tarafından paylaşılan videoların kalite değerlendirme ölçeklerinde sağlık profesyonelleri ve kişisel bloglardan daha yüksek puana sahip olduğu görülmüştür. İnternette güvenilirliği düşük bilgilerin yaygınlığı göz önüne alındığında tüketicilerin beslenme ve sağlık konusunda doğru bilgiler veren, alanında güvenilir videolara yönlendirilmesi gerekmektedir. Bu nedenle, YouTube™ platformuna bu alanlarda yüklenen videoların bir denetim sürecinden geçmesi faydalı olabilir. Ayrıca topluma internette sunulan bilgilerin güvenilirliği ve güvenilir kaynaklara ulaşma konusunda eğitimler verilebilir. Sağlık profesyonellerinin gıda katkı maddeleri konusunda bilgi düzeylerinin artırılması da toplumun bu konuda bilinçlendirilmesi için oldukça önemlidir. Bu konuda yapılacak kapsamlı müdahale çalışmalarına ihtiyaç vardır.

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KAPSAİSİN U87 İNSAN GLİOBLASTOMA HÜCRELERİNDE EPİTELYAL-MEZENKİMAL GEÇİŞİ REGÜLE EDEREK HÜCRE CANLILIĞINI BASKILAR

CAPSAICIN SUPPRESSES CELL VIABILITY BY REGULATING EPITHELIAL-MESENCHYMAL TRANSITION IN U87 HUMAN GLIOBLASTOMA CELLS

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ÖZ

Glioblastoma, merkezi sinir sistemini etkileyen en yaygın malign tümörlerden biri olarak öne çıkmakta ve etkili tedavi seçeneklerinin bulunmaması nedeniyle mevcut prognozu kötüdür. Homovanilik asidin bir türevi olan kapsaisinin, çeşitli kanser hücre dizileri üzerindeki anti-tümör etkileri belgelenmiştir. Epitelyal-mezenkimal geçiş, normal embriyogenez ve yara iyileşmesinin doğasında bulunan önemli bir moleküler ve hücresel süreçtir. Ayrıca çeşitli karsinom ve glioblastoma tiplerinde yaygın bir rol oynar. Bu çalışma, U87 glioblastoma hücre hatlarında kapsaisin tarafından indüklenen anti-tümör etkilerine epitelyal-mezenkimal geçişin potansiyel katılımını araştırmayı amaçladı. Başlangıçta kapsaisin tedavisinin hücre canlılığı üzerindeki etkisi 3-(4,5-dimetiltiyazol-2-il)-2,5-difenil tetrazolyum bromür analizi yoluyla değerlendirildi. Daha sonra hücresel proliferasyon ve sitotoksisite, bromodeoksiüridin analizi kullanılarak değerlendirildi. Daha ileri incelemeler, enzim-bağlı immünosorbent deneyi yoluyla N-kaderin, matriks metalloproteinaz-9, vimentin, transforme edici büyüme faktörü β, kaspaz 3, sitokrom c, glutatyon redüktaz, malondialdehit ve katalaz seviyelerinin belirlenmesini içeriyordu. Kapsaisin, U87 hücrelerinde anti-proliferatif etkiler sergileyerek, özellikle 50 µM'yi aşan konsantrasyonlarda hücre canlılığında konsantrasyona bağlı bir azalma sergiledi. Ek olarak kapsaisin uygulaması, U87 hücrelerinde N-kaderin, matriks metalloproteinaz-9, vimentin, transforme edici büyüme faktörü β, glutatyon redüktaz ve malondialdehit seviyelerinin azalmasına yol açarken, kaspaz 3, sitokrom c ve malondialdehit seviyelerinin artışına neden olmuştur.Sonuçlarımız kapsaisin uygulamasının U87 hücrelerinde epitelyal-mezenkimal geçişi düzenlemesinin yanı sıra apoptotik ve oksidatif süreçleri de tetikleyerek hücre canlılığını baskıladığını göstermiştir. Bu gözlem, epitelyal-mezenkimal geçiş inglioblastoma çoğalmasında ve migrasyonunda önemli bir rol oynadığını göstermektedir. Sonuç olarak, kapsaisin aracılı bu sinyal yolunun hedeflenmesi, glioblastoma tedavisinde umut verici bir terapötik yaklaşım olarak düşünülebilir.

Anahtar kelimeler: Epitelyal-mezenkimal geçiş, glioblastoma, kapsaisin

ABSTRACT

Glioblastomast ands out as one of the most prevalent malignant tumors affecting the central nervous system, and its current prognosis is unfavorable due to the lack of effective treatment options. Capsaicin, a derivative of homovanillic acid, has been documented for its anti-tumor effects across various cancer cell lines. Epithelial-to-mesenchymal transition is a pivotal molecular and cellular process inherent to normal embryogenesis and wound healing. Moreover, it plays a widespread role in diverse carcinoma and glioblastoma types. This study sought to explore the potential involvement of epithelial-to-mesenchymal transition in the anti-tumor effects induced by capsaicin in U87 glioblastoma cell lines. Initially, the impact of capsaicin treatment on cell viability was assessed through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide analysis. Subsequently, cellular proliferation and cytotoxicity were evaluated using bromodeoxyuridine analysis. Further examinations involved determining the levels of N-cadherin, matrix metalloproteinase-9, vimentin, transforming growth factor β, caspase 3, cytochrome c, glutathione reductase, malondialdehyde and catalase through enzyme-linked immunosorbent assay. Capsaicin exhibited anti-proliferative effects in U87 cells, displaying a concentration-dependent reduction in cell viability, particularly with concentrations exceeding 50 µM. Additionally, capsaicin administration led to decreased of N-cadherin, matrix metalloproteinase-9, vimentin, transforming growth factor β, glutathione reductase and catalaselevels in U87 cells, while increasing caspase 3, cytochrome c and malondialdehyde levels.Our results showed that capsaicin treatment not only regulates epithelial-to-mesenchymal transition in U87 cells, but also suppresses cell viability by triggering apoptotic and oxidative processes. This observation suggests that epithelial-to-mesenchymal transition plays a pivotal role in the proliferation and migration of glioblastoma. Consequently, targeting this capsaicin-mediated signaling pathway could be considered a promising therapeutic approach in the treatment of glioblastoma.

Keywords: Epithelial-mesenchymal transition, glioblastoma, capsaicin

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GİRİŞ

Epitelyal-mezenkimal geçiş (EMT), polarize epitel hücrelerinin çok sayıda biyokimyasal değişikliğe uğraması için uyarıldığı biyolojik bir süreçtir.[1] EMT yara iyileşmesi, embriyonik gelişim ve dokunun yeniden yapılanması için gerekli sinyalizyon mekanizmasıdır. Patolojik bir süreç olarak EMT, canlılıkta bir kayıp olmaksızın epitelyal tümör hücrelerinde göç ve invaziv yetenekleri de indükler.[2] EMT süreci, tümör hücrelerinin bazal membrandan ayrılmasını içerir. Merkezi sinir sistemi (CNS) bu kritik doku bileşeninden yoksun olmasına rağmen, CNS kanserleri ve diğer kanser türleri arasında temel invazif mekanizmalar örtüşmektedir.[3] Diğer kanserlerde EMT'yi tetikleyen faktörler aynı zamanda GBM'lerdeki mezenkimal özellikleri de aktive edebilir. Glioblastoma (GBM)mezenkimal alt tipi tipik olarak nöral kök hücre belirteçlerini eksprese eder ve agresif bir fenotiple ilişkilidir.[4] Kök hücre belirteçlerini eksprese eden GBM hücreleri oldukça invazivdir ve *in vitro* ve klinik ortamda kemoterapi ve radyoterapiye dirençlidir.[5]

GBM'ler histopatolojik özelliklerine göre sınıflandırılır; bu özellikler klinisyenlerin iki hücresel soy (astrositik ve oligodendrositik) ile dört malignite derecesi (derece I ila IV) arasında ayrım yapmasına olanak tanır.[6] Derece IV'ün en kötü huylu formu, astrositik soydaki progenitör veya kök hücrelerden kaynaklanan GBM'dir. Pronöral alt tip pozitif prognoz ile ilişkilidir, mezenkimal alt tip ise yüksek oranda invazif bir doğaya ve kötü prognoza sahip, daha yüksek oranda döngüsel hücre ve neoanjiyogenez ile karakterize edilir.[7] Ayrıca tümörlerin mezenkimal olmayan alt tipleri tipik olarak nüks sırasında mezenkimal özellikler kazanır.[8] Mezenkimal alt tipe doğru bir kayma, daha agresif bir doğa kazanmak için EMT uygulanan kanser hücrelerine benzer şekilde, hastalığın ilerlemesinde yaygın bir model gibi görünmektedir.[9]

Kapsaisin, farmakolojik önemi olan biyolojik etkileri açısından kapsamlı bir şekilde araştırılan kırmızı biberin (*Capsicumannuum*) keskin bir alkaloididir.[10] Kapsaisinin anti-inflamatuar ve anti-oksidatif stres aktiviteleri gibi faydalı etkilere sahip olduğu bilinmektedir[11], ancak kanser hücrelerinin (EMT) yoluyla aktivasyonu gibi olumsuz etkileri de vardır.[12] Kapsaisinin, Hedgehog sinyal yolunu düzenleyerek ve *in vivo* EMT'yi önleyerek kolanjiyo karsinom karsinogenezini zayıflattığı bildirildi.[13] Bu raporlar kapsaisinin EMT üzerinde hücreye özgü etkileri indüklediğini göstermektedir.

Bu nedenle, bu çalışmada U87 insan GBM hücrelerindeki N-kaderin, matriks metaloproteinaz-9 (MMP-9), vimentin ve dönüştürücü büyüme faktörü β (TGF-β) gibi EMT biyobelirteçleri üzerinde kapsaisinin rolünü araştırmayı amaçladık. Aynı zamanda, kaspaz 3 ve sitokrom c gibi apoptotik beliteçlerin yanında prooksidan-oksidan dengenin durumuna bakabilmek için glutatyon redüktaz, malondialdehitve katalaz seviyelerinin ölçümünü gerçekleştirdik. Böylece kapsaisin kaynaklı anti-proliferatif etkilerin altında yatan olası moleküler mekanizmaları açıkladık.

GEREÇ VE YÖNTEM

Hücre Kültürü

U87 GBM hücre hattı Amerikan Tipi Kültür Koleksiyonundan temin edildi. Bu hücre hatları, 2 mM glutamin, %10 fetal dana serumu (FBS), 100 U/ml penisilin ve 100 ug/ml streptomisin ile desteklenmiş Dulbecco'nun değiştirilmiş Eagle ortamında (DMEM) yetiştirildi. Hücreler %5 CO_2 içeren bir inkübatör içerisinde 37°C sıcaklıkta tutuldu.

Hücre Canlılık ve Proliferasyon Analizleri

Hücre canlılığını değerlendirmek için kolorimetrik 3-(4,5-dimetiltiyazol-2-il)-2,5-difeniltetrazolyum bromür (MTT) tahlili kullanıldı. Kısaca, U87 hücreleri (3×10^4) 96 kuyucuklu plakalara ekildi ve 37°C, %5 CO_2'de 24 ve 48 saat boyunca farklı kapsaisin konsantrasyonları ile (0 ila 800 µM) ile kültürlendi. İşlemin sonunda numunelere 0.8 mg/ml MTT ilave edildi ve 3 saat süreyle inkübe edildi. Daha sonra süpernatanlar atıldı ve 100 µl/ kuyucuk DMSO ile çözünen renkli formazan kristalleri, mikro plaka okuyucusu (BioTek) tarafından 570 nm'de okundu. Tedavi edilmeyen kontrol grubundaki hücre canlılığı %100 olarak kabul edildi ve kapsaisin ile tedavi edilen hücrelerin canlılığı kontrol grubuna göre hesaplandı.

Kapsaisinin, ticari olarak temin edilebilen 5-bromo-2'-deoksiüridin (BrdU) kitini (2750; Sigma-Aldrich) kullanarak 24 kuyucuklu plakalarda kültürlenen U87 hücrelerinin (3×10^5) proliferasyonu üzerindeki etkisini analiz ettik. Hücreler, MTT analizi sonuçlarına göre belirlenen kapsaisin konsantrasyonları (93.7 µM, 115.8 µM ve 142.6µM) ile 24 saat boyunca inkübe edildi ve hücre çoğalması, hücresel replikasyon sırasında BrdU birleştirme tahliline dayalı olarak üreticinin talimatlarına göre kolorimetrik olarak ölçüldü. Absorbans değerlerinin analizi, bir Epoch mikroplaka okuyucu (BioTek) ile 450 nm'de gerçekleştirildi.

EMT Biyobelirteçlerin Analizi

N-kaderin (SEB481Hu), MMP-9 (SEA553Hu), vimentin (SEB040Hu) ve TGF-β (SEA124Hu) seviyeleri enzim bağlantılı immünosorbent tahlili (ELISA) kitleri kullanılarak değerlendirildi. üretici tarafından sağlanan talimatlara uygun olarak. Bu analizleri gerçekleştirmek için U87 hücreleri, 1×10^4 hücre yoğunluğunda 96 kuyucuklu plakalara ekildi ve ardından 24 saat boyunca kapsaisin ile inkübe edildi. İnkübasyon periyodunun ardından her numunenin absorbansı, önerilen dalga boyunda bir mikroplaka okuyucuda ölçüldü.

Hücre apoptoz tespiti

ELISA için, 96 kuyucuklu plakalara ekilen hücreler (kuyucuk başına 1×10^4), 24 saat boyunca kapsaisine maruz bırakıldı. Üreticinin talimatlarına göre sitokrom c (SEA594Mi) ve kaspaz 3 (SEA626Hu) kitleri kullanılarak hücre apoptozu tespit edildi. Hücreler, oda sıcaklığında 30 dakika boyunca 200 µLlizis tamponu ile parçalandı. Daha sonra hücre lizatları 200xg'de 10 dakika boyunca 4 °C'de santrifüjlendi. Yirmi mikrolitre süpernatan, streptavidin kaplı bir mikro kuyucuklu plakaya aktarıldı, her bir çalışma reaktifleri eklendi ve plaka, oda sıcaklığında 2 saat süreyle inkübe edildi. Kuyucuklar üç kez yıkandı ve subtrat ve durdurma çözeltileri eklenerek absorbans değerleri 450 nm'de ölçüldü.

Oksidatif ve Anti-oksidan Durumun Analizi

Hücreler 96 kuyucuklu bir plakaya 1×10^4/kuyucuk yoğunlukta ekildi ve 24 saat süreyle inkübe edildi. Hücreler daha sonra 24 saat süreyle kapsaisin konsantrasyonları ile inkübe edildi. Hücrelerdeki oksidatif hasar tespit etmek içinglutatyon redüktaz (SEB314Hu), katalaz (SEC418Hu) ve malondialdehit (MBS728071) kitleri

kullanılarak bir ELISA analizi yapıldı. Kısaca hücreler, oda sıcaklığında 30 dakika boyunca 200 µL lizis tamponuyla parçalandı. Lizat 10 dakika boyunca santrifüjlendi ve toplanan 20 µL süpernatan, çalışma reaktifleri ile oda sıcaklığında 2 saat süreyle inkübe edildi. İnkübasyon tamponu ile üç kez yıkandıktan sonra, substrat solüsyonu ilave edildi ve oda sıcaklığında 15 dakika inkübe edildi. Ardından, durdurma solüsyonu eklenerek absorbans değerleri bir ELISA okuyucu kullanılarak ölçüldü.

İstatistiksel Analiz

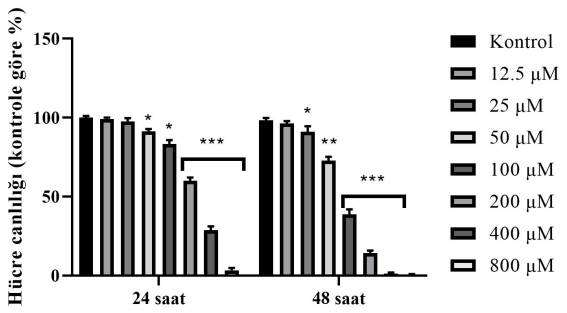
İstatistiksel analiz Graph Pad Prism 8 (Graph Pad Inc., ABD) kullanılarak yapıldı. Deneyler üç kez tekrarlandı. Veriler ortalama ± standart sapma (SD) olarak sunuldu. Deney gruplarını karşılaştırmak için tek yönlü varyans analizi (ANOVA) kullanıldı ve ardından çoklu grup karşılaştırmaları için Tukey post hoc testi kullanıldı. P değeri 0.05'ten küçük olduğunda istatistiksel anlamlı kabul edildi.

BULGULAR

Kapsaisinin hücre canlılığı üzerindeki etkileri

Kapsaisin, kontrol gruplarına kıyasla U87 hücrelerinde konsantrasyona ve zamana bağlı bir azalma ile hücre canlılığını inhibe etti. Şekil 1'de gösterildiği gibi, U87 hücrelerinin kapsaisin (0-800 µM) ile 24 ve 48 saat süreyle işlenmesi hücre canlılığını baskıladı. Bununla birlikte, 24 saat boyunca 12.5µM ila 25µM konsantrasyon aralığında kapsaisin tedavisi, U87 hücre canlılığını önemli ölçüde azaltmadı (p>0.05). MTT sonuçlarına göre, kontrol grubu ile karşılaştırıldığında 24 saatlik 50 µM, 100 µM, 200 µM, 400 µM ve 800 µM kapsaisin tedavisi, U87 hücre canlılığını sırasıyla %9.4, %17.5, %40.2, %71.6 ve %97.1 oranında azalttı (p<0.01 ve p<0.001). Ek olarak, 48 saat boyunca 25 µM ve üzeri kapsaisin konsantrasyonlarında U87 hücre canlılığı konsantrasyona bağlı bir şekilde inhibe edildi. Sonuçlarımıza göre de, 48 saatte boyunca 25 µM, 50 µM, 100 µM, 200 µM ve 400 µM kapsaisin maruziyeti U87 hücre canlılığının inhibisyon oranları sırasıyla %12.5, %26.4, %59.6, % 86.1 ve %98.5 (p<0.01 ve p<0.001). Dahası, 48 saat boyunca 800 µM kapsaisin maruziyetinde hücre canlılığı yok denecek kadar azdı. MTT sonuçlarına göre U87 hücreleri için IC50 ve IC25 kapsaisin değerleri sırasıyla 93.7 µM ve 142.6µM µM olarak hesaplandı. Ayrıca, diğer biyokimyasal analizler sırasında 24 saat boyunca 93.7 µM,115.8 µM (ara konsantrasyon olarak) ve 142.6µM konsantrasyonları kullanılmıştır.

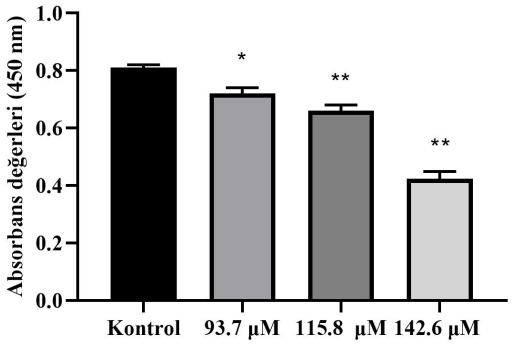
Kapsaisinin hücre proliferasyonu üzerindeki etkisi



Şekil 1: Kapsaisin, U87 hücrelerindeki hücresel canlılığı olan etkileri. *p<0.05, **p<0,01 ve ***p<0.001, kontrol grubuyla karşılaştırıldığında

Kapsaisinin U87 hücrelerinin proliferasyonu üzerindeki etkilerini BrdU analizi ile belirledik. MTT sonuçlarıyla bağlantılı olarak, 24 saat boyunca 93.7 µM,115.8 µM ve 142.6 µM kapsaisin konsantrasyonlarıyla tedavi edilen U87 hücrelerinin çoğalması önemli ölçüde azaldı (p< 0.001; Şekil 2). Ek olarak, U87 hücrelerinde 93.7 µM, 115.8 µM ve 142.6 µM kapsaisin uygulaması, hücre proliferasyonu sırasıyla %21.8, %33.1 ve %56.2 oranında azalttı (p<0.001).

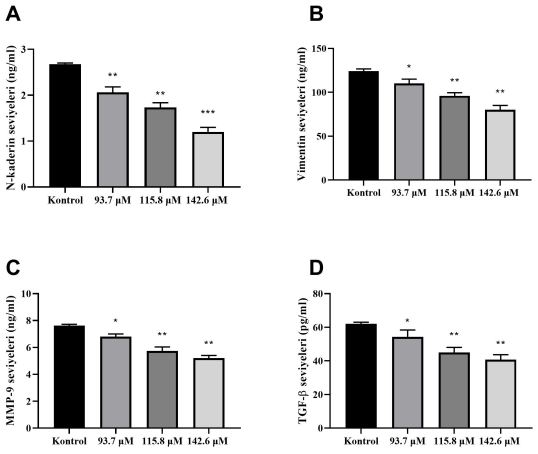
Kapsaisinin EMT biyobeliteçleri üzerindeki etkileri



Şekil 2: Kapsaisinin U87 hücrelerindeki proliferasyon üzerine etkileri. *p<0.05 ve **p<0.01, kontrol grubuyla karşılaştırıldığında

Şekil 3A, 3B, 3C ve 3D'de sunulan bulgular, kapsaisin tedavisinin U87 hücrelerinde çeşitli EMT biyobelirteçleri üzerinde önemli regülatif etkilere sahip olduğunu göstermektedir. Kapsaisin tedavisine yanıt olarak U87 hücrelerindeki N-kaderin, MMP-9, vimentin ve TGF-β düzeylerinde gözlemlenebilir değişiklikler oldu. Kapsaisin tedavisi U87 hücrelerindeki N-kaderin, MMP-9, vimentin ve TGF-β düzeylerinde konsantrasyon bağımlı şekilde düşüşe neden oldu. Dikkat çekici bir şekilde ELISA analiz sonuçları, kapsaisin maruziyeti sonrasında bu biyobeliteçlerin protein seviyelerinde önem yüzdesel değişiklikleri ortaya çıkarmış oldu.

Kapsaisinin apoptoz üzerindeki etkileri

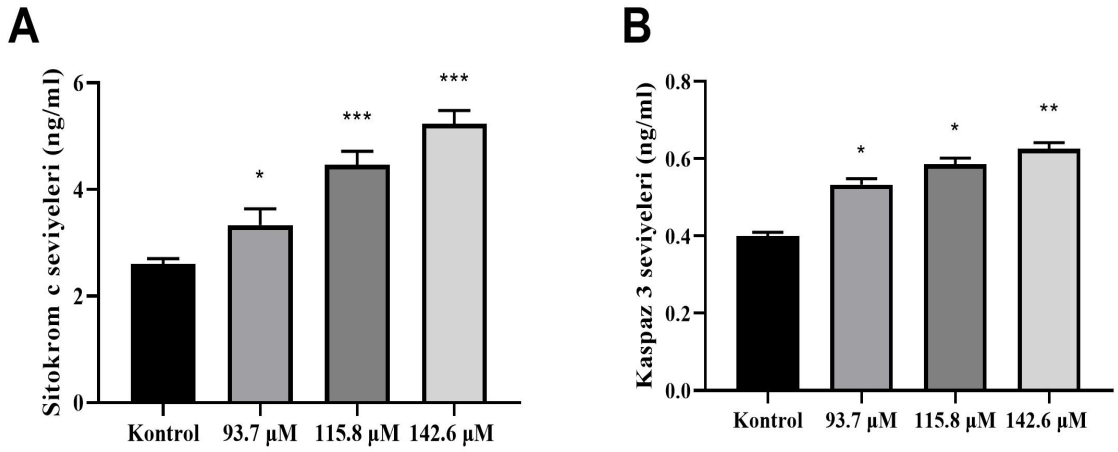


Şekil 3: U87 hücrelerinde kapsaisin maruziyeti EMT biyobelirteçlerinin seviyeleri düşürdü.(A) U87 hücrelerindeki N-kaderin seviyeleri; (B) U87 hücrelerindeki vimentin seviyeleri; (C) U87 hücrelerindeki MMP-9 seviyeleri; (D) U87 hücrelerinde TGF-β seviyeleri. *p<0.05, **p<0.01 ve ***p<0.001, kontrol grubuyla karşılaştırıldığında

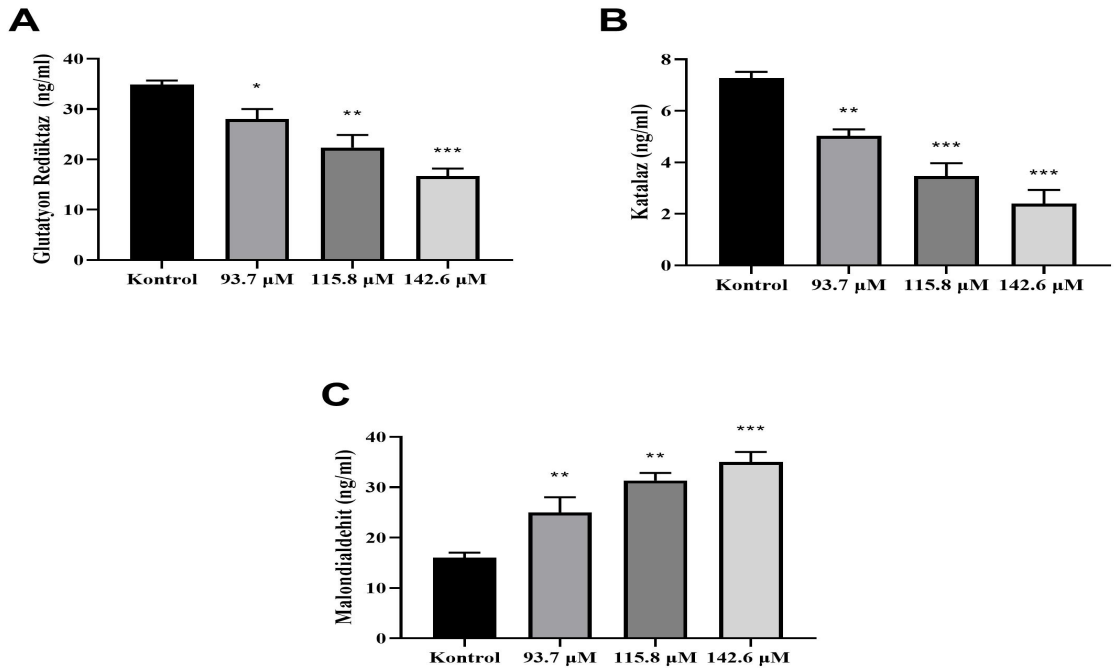
Kapsaisin tedavisinden sonra, U87 hücrelerindeki programlanmış hücre ölümü olan apoptotik süreçlerin artışan neden olmuştur (Şekil 4A ve 4B). U87 hücreleri 24 saat boyunca çeşitli konsantrasyonlarda kapsaisin ile tedavi edildikten sonra hücreler toplandı ve sitokrom c ve kaspaz 3 seviyeleri ELISA ile analiz edildi. Veriler, kapsaisin'in sitokrom c ve kaspaz-3 aktivitesini konsantrasyona bağlı bir şekilde indüklediğini gösterdi. Sonuçlarımız, apoptoz indüksiyonunun bir işareti olarak sitokrom c ve kaspaz 3 seviyelerindeki artışının, U87 hücrelerinin 93.7, 115.8 ve 142.6 µM kapsaisin ile tedavi edilmesinden sonra kontrol grubuyla karşılaştırıldığında önemli ölçüde arttığını ortaya çıkardı ($p<0.05$) .

Kapsaisinin oksidatif stres üzerindeki etkileri

Kapsaisinin U87 hücrelerinde anti-proliferastif etkilerinin oksidatif stres ile olan ilişkisini incelemek için de glutatyon redüktaz, katalaz ve malondialdehit seviyelerini ölçümünü gerçekleştirdik. U87 hücreleri, 24 saat boyunca farklı konsantrayonlardaki kapsaisin ile muamele edildi. Glutatyon redüktaz ve katazlar seviyelerindeki düşüş, kapsaisinin U87 hücrelerinde anti-oksidan savunma sistemini baskıladığını gösterdi (Şekil 5A ve 5B). Ek olarak, Şekil 5C'de gösterildiği gibi kapsaisin uygulaması, lipit peroksidasyonunun önemli bir göstergesi olan malondialdehit seviyelerinde artışa neden olarak oksidatif stresin U87 hücrelerinde indüklediğini gösterdi.



Şekil 4: U87 hücrelerinde kapsaisin maruziyetinin apoptoza olan etkileri.(A) U87 hücrelerindeki sitokrom c seviyeleri; (B) U87 hücrelerindeki kaspaz 3 seviyeleri. *p<0.05, **p<0.01 ve ***p<0.001, kontrol grubuyla karşılaştırıldığında



Şekil 5: U87 hücrelerinde kapsaisin maruziyetinin oksidatif stres ve anti-oksidan mekanizmalar üzerindeki etkileri.(A) U87 hücrelerindeki glutatyon redüktaz seviyeleri; (B) U87 hücrelerindeki katalaz seviyeleri; (C) U87 hücrelerindeki malondialdehit seviyeleri. *p<0.05, **p<0.01 ve ***p<0.001, kontrol grubuyla karşılaştırıldığında

TARTIŞMA

Kanser, Dünya Sağlık Örgütü'ne (WHO) göre dünya çapında hastalık ve ölümlerin önde gelen nedenlerinden birini temsil eden küresel bir sağlık yüküdür. Bitkilerden ekstrakte edilen biyoaktif doğal ürünler, nispeten toksik olmayan ve aktif profilleri nedeniyle kanser tedavisi için yaygın olarak yeni terapötik ve önleyici ilaçlar olarak kabul edilmektedir.[14] Bunlar arasında, acı biberden elde edilen umut verici bir anti-tümör ajanı olan kapsaisinin, *in vitro* ve *in vivo* olarak çeşitli kanserlerde hücre büyümesini ve metastazı inhibe ettiği doğrulanmıştır.[15,16] Ancak kapsaisinin birçok kanser hücresindeki anti-proliferatif, anti-metastatik ve anti-anjiyojenik etkileri kapsamlı bir şekilde araştırılmış olmasına rağmen kanser metabolizması ile ilgili süreçler henüz tam olarak anlaşılamamıştır. Bu çalışmada, kapsaisinin *in vitro* U87 hücre hatlarında EMT'yi inhibe ettiğini ortaya çıkardık. Dahası, çeşitli kapsaisin konsantrasyonları ile tedavi edilen U87 hücrelerinde 48 saate kadar sitotoksisite analizleri gerçekleştirdik ve kapsaisinin EMT biyo belirteçleri üzerindeki etkilerini analiz ettik.

EMT, epitelyalden iğ şeklindeki mezenkimal benzeri hücrelere doğru morfolojik değişiklikler, artan hücre boyutu, integrin ekspresyonundaki değişikliklerin bir sonucu olarak hücre yapışmasının kaybı, özellikle α5 ve β1 integrinlerin aşırı ekspresyonu, artan invazivlik ve özellikle vimentin mezenkimal belirteçlerin ekspresyonu ile karakterize edilir.[17] Önceki çalışmada, kapsaisnin kolon kanseri hücrelerinde EMT'yi indüklediği bulunmuştur.[18] Bir başka çalışmada ise, 5637 ve T24 mesane kanseri hücrelerinde kaspsaisin maruziyetinin, artan hücre boyutu ve mezenkimal benzeri morfoloji, vimentin, α5 ve β1 integrin alt birimlerinin ve integrin benzeri kinaz (ILK) ve anti-apoptotik Bcl-2 proteinlerinin gelişmiş ekspresyonunu ve E-kaderinin seviyelerinde düşüş olduğu rapor edilmiştir.[19]

EMT, tümör hücrelerinin yeniden programlandığı ve hücre iskeletinin yeniden düzenlenmesi, hücre bağlantılarının kaybı ve ekstraselüler matriksin yeniden modellenmesi yoluyla epitelyal bir fenotipten invazif mezenkimal benzeri bir fenotipe dönüştürüldüğü bir sistemdir.[20] Ek olarak renal hücreli karsinom (RCC) hücre dizileri 786-O ve CAKI-1'de kapsaisinin rolünü araştırılmış ve kapsaisin uygulanan RCC hücrelerinin canlılığının, göçünün ve istilasının regüle ederek EMT sürecini inhibe ettiğini gösterilmiştir.[21] Bu çalışma araştırmacılar, kapsaisinin, E-kaderin (epitelyal belirteç) seviyelerini arttırdığını ve N-kaderin ve vimentin (mezenkimal belirteçler) seviyelerini düşürdüğünü doğrulamıştır; bu da, EMT'nin, kapsaisin ile tedavi edilen RCC hücrelerinde inhibe edildiğini ortaya koydu. Ayrıca, meme kanseri MDA-MB-231 hücrelerinde kapsaisinin, c-Src, FAK ve paxillinin fosforilasyonunu inhibe ederek ve MMP-2 ve MMP-9 ekspresyonlarını baskılayarak hücre göçünü ve istilasını baskıladığı bulundu.[22] Fare prostatının transgenik adenokarsinomunda (TRAMP) kapsaisin tedavisi, karaciğerde ve gastrointestinal sistemde belirgin patolojik toksisitelere yol açmadan metastatik yükte önemli bir azalma gösterdi; bu, p27'deki bir azalmayla ilişkilendirildi.[23] Ling ve ark., GBM hücrelerinde, TGF-β2'nin EMT'yi kontrol etmek için kritik bir öneme sahip olduğunu rapor etmişlerdir.[24] Yukarıda belirtilen çalışmalarla uyumlu bir şekilde, U87 hücrelerinde kapsaisin uygulamasından sonra N-kaderin, MMP-9, vimentin ve TGF-β düzeylerinin azaldığını tespit ettik. Ayrıca MTT analizlerine göre, U87 hücreleri için kapsaisinin IC50'sinin 24 saat boyunca 121.6 μM olduğunu olduğunu bulduk. U87 hücre hattında kapsaisin tedavisi, BrdU birleşme analizine göre hücre proliferasyonunda konsantrasyona bağlı bir azalmaya neden olduğunu da ortaya koyduk. Bu sonuçlar, kapsaisinin insan U87 hücrelerinde EMT sinyalizasyonunu regüle ederek hücre proliferasyonunu baskıladığını düşündürebilir.

Apoptoz, kanser gelişimi ve ilerlemesine karşı önemli bir engeldir ve apoptotik sinyal kaybı, malignite ile yüksek oranda ilişkilidir.[25] Birçok kanser türü apoptotik yolakları bozar ve kanser hücrelerini apoptoza dirençli hale getiren anti-apoptotik yolları güçlendirir. Kapsaisinin, pankreas, kolon, prostat, karaciğer, özofagus, mesane, deri dahil olmak üzere birçok farklı kanser hücre dizisinde apoptozu indüklediği gösterilmiştir.[26] İçsel mitokondriyal ölüm yolu ve dışsal ölüm reseptörü yolu, uygulayıcı/efektör kaspazları aktive eden ve programlanmış hücre ölümüne yol açan iki ana sinyal sistemidir. Özellikle mitokondriyal yol, apoptozun tam olarak yürütülmesiyle meşguldür, bu nedenle mitokondri, apoptotik mekanizmanın 'bekçisi' olarak adlandırılmıştır ve mitokondriyal ölüm yolunun proteinleri ve yolları, yeni terapötik tedaviler için umut verici hedefler haline gelmiştir.[27] Kapsaisinin, farklı kanser hücre hatlarında apoptozu başlatmak için mitokondriyal ölüm yolunda yer alan çeşitli proteinleri hedeflediği gösterilmiştir. Örneğin kapsaisin tedavisi, içsel ve dışsal apoptotik yolların aktive ettiği ve kaspaz-9 ve -3 aktivasyonuna yol açan anti-apoptotik protein, B hücreli lenfoma 2'nin ekspresyonunu bastırğı ve mitokondriyal membran potansiyelinin kaybını takibensitokrom c salınımının arttığı gösterilmiştir.[28]

Mitokondri, mitokondriyal solunum sırasında oksijenin eksik indirgenmesi nedeniyle üretilen reaktif oksijen türlerinin (ROS) ana fizyolojik kaynağıdır.[29] Bazı patolojik durumlarda aşırı ROS üretimi apoptoza neden olur. Normal koşullar altında mitokondri, aşırı ROS oluşumunu ve oksidatif hasarı önleyen yeterli düzeyde antioksidan içerir. Bununla birlikte, ROS üretiminin arttığı veya anti-oksidan seviyelerinin tükendiği durumlarda oksidatif stres, protein oksidasyonuna ve lipit peroksidasyonuna neden olur ve bu da mitokondriyal membran, proteinler ve DNA'da hasara yol açar.[30] Kanser hücreleri, tümör büyümesini sürdüren ve bu hücreleri pro-apoptotik sinyallere karşı koruyan, böylece tümörün ilerlemesini teşvik eden gelişmiş bir yapısal oksidatif stres seviyesi geliştirir. İlginçtir ki, Zhang ve meslektaşları kapsaisin tedavisinin, normal asiner hücreleri etkilemeden hem AsPC-1 hem de BxPC-3 hücrelerinde mitokondriyal membran potansiyelini önemli ölçüde azalttığını gösterdi.[31] Bir başka çalışmada, kapsaisin U251 hücrelerindeki apoptotik etkileri, ROS üretimi, hücre içi kalsiyum artışı, ekstraselüler matriks bozulması ve sitokrom c'nin sitozole salınması ve kaspazkas kadının aktivasyonu ile ilişkiliydi.[32] Bu çalışma, acı biberde en çok bulunan ikinci kapsaisinoid olan kapsaisinin, U251 insan GBM hücrelerine karşı antikanser ajanları olabileceğini gösterdi. Kapsaisinin GBM hücrelerinde oksidatif stres aracılığıyla mitokondriyal bütünlüğü bozarak apoptozu indüklediğini, bunun glutatyon ve katalaz gibi anti-oksidanların seviyelerinin düşmesi ve kaspaz3'ü aktive etmek için sitozole

sitokrom c salınımı ile ilişkili olduğunu gösterdi.

Kapsaisin, ortalama 60°C erime noktasına ve 305.4 kDa moleküler ağırlığa sahip, yağda çözünen bir kapsaisinoiddir. *İn vivo* çalışmalar, oral alımdan sonra kapsaisin emiliminin %50 ila %90 arasında değiştiğini göstermektedir.[33] Dahası kapsaisinin *in vivo* çalışmaların da gösterildiği gibi, kan-beyin bariyerini etkili bir şekilde geçer. İntravenöz uygulamadan sonra, bileşiğin beyinde ve omurilikte serumla karşılaştırıldığında 5 kat daha yüksek konsantrasyonları rapor edilmiştir.[34] Ek olarak hayvan çalışmalarında kapsaisinin subkutan uygulamadan sonra plazmada, beyinde ve omurilikte tespit edilebildiği gösterilmiştir.[33] Kapsaisinin oral yoldan uygulanmasına yönelik farmasötik formülasyonlar, kırmızı biber içeren kapsüller formunda mevcuttur.[35] Kapsaisinin oral uygulaması için terapötik doz belirlenmemiştir, ancak ticari olarak temin edilebilen kapsüllerin etiketlerinde belirtilen genel olarak önerilen günlük doz, %0.25 kapsaisin içeren 1350-4000 mg kırmızı biberdir.[36] Bu doz aralığının insanlarda enerji harcamasını, yağ oksidasyonunu, termojenezi artırdığı, iştahı azalttığı ve toksik bir yan etkiye neden olmadığı gösterilmiştir.[37] Farklı bir çalışmada baş ağrısı hastalarında intranazal kapsaisin (10 mM) uygulamasının ağrı ataklarının sıklığını azalttığı bulunmuştur.[38] Yukarıda bahsi geçen çalışmalara göre, hidrofobik ve lipofilik karaktere sahip olan kapsaisinin kan beyin bariyerini geçtiği yapılan çalışmalar ile de ortaya konmuştur. Ek olarak, sonuçlarımız literatür ile de tutarlı şekilde, hücre tipine bağlı olarak 100 ila 500 µM aralığındaki kapsaisinin, 40'tan fazla farklı tipte kanser hücre hattında hücre proliferasyonunu baskıladığı bildirilmiştir.[39,40] Dahası, *in vitro* analizler sırasında kullandığımız kapsaisin konsantrasyonlarının kabul edilebilir aralıkta olduğunu da doğrulamış olduk. Kuşkusuz kapsaisinin sağlık üzerindeki etkileri çoğunlukla olumludur. Ancak, kapsaisinin nörodejeneratif hastalıklar üzerindeki etkilerini aydınlatmayı amaçlayan daha ileri klinik öncesi araştırmalara ihtiyaç vardır.

SONUÇ

Sonuç olarak, GBM hücrelerinde kapsaisin, N-kaderin, MMP-9, vimentin ve TGF-β düzeylerinin düşürerek EMT'nin inhibisyonu yoluyla hücre canlılığı ve proliferasyonunu baskılamıştır. Ancak, bu çalışmanın en büyük limitasyonlarından biri kapsaisinin tümör dışı hücrelerdeki ve *in vivo* modellerdeki etkilerinin analiz edilmemiş olmasıdır. Diğer bir sınırlılık ise çalışmamızın bir ön araştırma olması nedeniyle 24 saatlik kapsaisin tedavisinin etkilerinin araştırılmış, uzun vadeli etkilerinin araştırılmamış olmasıdır. Bu nedenle kapsaisinin farklı kanser türlerinde diğer EMT biyobelirteçler üzerindeki etkilerini araştırmak için daha ileri çalışmalara ihtiyaç vardır.

Etik Komite Onayı: Ticari olarak temin edilen hücre hatları in vitro deneylerde kullanıldığı için etik onay gerekmemektedir. Deneysel çalışmalarda sırasında herhangi bir hayvan ve insan dokusu kullanılmamıştır.

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Yazar Katkıları: Fikir- CH; Tasarım- CH; Denetleme- CH; Kaynaklar- CH; Malzemeler- CH; Veri Toplanması ve/veya işlenmesi- CH; Analiz ve/veya yorum- CH; Literatür taraması- CH; Yazıyı yazan- CH; Eleştirel inceleme- CH.

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Informed Consent: There is no need to obtain informed consent.

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Author Contributions: Concept- CH; Design- CH; Supervision- CH; Resources- CH; Materails- CH; Data Collection and/or Processing- CH; Analysis and/or Interpretation- CH; Literature Search- CH; Writing Manuscript- CH; Critical Review- CH.

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KANSER TEDAVİSİ GÖREN ÇOCUKLARIN ORAL MUKOZİT YÖNETİMİNDE HEMŞİRELİK BAKIM UYGULAMALARI: SİSTEMATİK BİR DERLEME
NURSING CARE PRACTICES IN THE MANAGEMENT OF ORAL MUCOSITIS OF CHILDREN WITH CANCER TREATMENT: A SYSTEMATIC REVIEW

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ÖZ

Oral mukozit, çocuklarda sitotoksik kemoterapinin önemli bir komplikasyonudur. Oral mukozitin pediatrik hastalarda önemli morbidite ile ilişkili ve tipik olarak çok ağrılı ve rahatsız edici olduğu bilinmektedir. Mukozit, geleneksel kemoterapi alan hastaların pek çoğunda görülmektedir. Oral mukozitin hastaneye yatışı gerektirecek kadar şiddetli, besin alımının, ağız bakımının ve yaşam kalitesinin azalmasına yol açacak kadar da etkili olduğu bilinmektedir. Günümüzde oral mukozitin tedavi ve bakımında pek çok yöntem kullanılmaktadır. Yapılan bu sistematik incelemenin amacı, 0-18 yaş aralığında kanser tedavisi gören çocuklarda gelişen oral mukozit yönetiminde kullanılan hemşirelik bakım uygulamalarının son 3 yıldaki literatüre katkısını incelemektir. PubMed, Scopus, Google Scholar, Science Direct, Ovid Medline, EBSCO veri tabanları kullanılarak, 2019-2022yıllarıarasında oral mukozit yönetiminde kullanılan hemşirelik bakım uygulamalarını inceleyen Meta-analiz ve randomize kontrollü çalışmalar geriye doğru incelenmiştir. Kullanılan yöntemlerde hemşirelere çok önemli görev ve sorumlulukların düştüğü görülmüştür. Hemşirelerin randomize kontrollü çalışmalar yaparak daha fazla kanıtlar sağlaması çocuklar için çok önemli bir sorun olan oral mukozitin yönetiminde alternatif yollar üreteceğini göstermektedir.

Anahtar kelimeler: Çocuk, hemşirelik, kanser, oral mukozit, yönetim.

ABSTRACT

Oral mucositis is a significant complication of cytotoxic chemotherapy in children. Oral mucositis is known to be associated with significant morbidity in pediatric patients and is typically very painful and irritated. Mucositisis seen in many patients receiving conventional chemotherapy. It is known that oral mucositis is severe enough to require hospitalization and effective enough to cause a decrease in food intake, oral care and quality of life. Today, many methods are used in the treatment and care of oral mucositis. The purpose of this systematic review is to examine the contribution of nursing care practices used in the management of oral mucositis in children receiving cancer treatment between the ages of 0-18 to the literature in the last 3 years. Meta-analysis and randomized controlled studies examining nursing care practices used in the management of oral mucositis between 2019 and 2022 were retrospectively examined using Pub Med, Scopus, Google Scholar, Science Direct, Ovid Medline, EBSCO databases. It has been observed that nurses have very important duties and responsibilities in the methods used. Providing more evidence by conducting randomized controlled studies shows that nurses will produce alternative ways to manage oral mucositis, which is a very important problem for children.

Keywords: Child, nursing, cancer, oral mucositis, management.

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GİRİŞ

Oral mukozit (OM) kanser tedavisinin bir sonucu olarak ağız mukozasında meydana gelen hasar ve iltihaplanmadır.[1] OM, çocuklarda sitotoksik kemoterapinin önemli bir komplikasyonudur.[2] Mukozit, geleneksel kemoterapi alan hastaların %20 ila %40'ında ve hematopoetik kök hücre nakli için ön şartlandırma olarak yüksek dozda kemoterapi alanların%80'inde görülmektedir.[3]Çocukların yetişkin hastalardan daha fazla kemoterapi kaynaklı mukozit prevalansına sahip olduğu bildirilmektedir.[3,4] OM gelişimini, kemoterapik ajanın dozunun yanı sıra türü ve eşzamanlı radyoterapi uygulaması da etkilemektedir.[5] Ayrıca, hastaya verilen antikolinerjik ve steroid grubu ilaçlar ile oksijen tedavisi de OM 'ye neden olabilecek durumlar arasındakabul edilmektedir.[5] OM'nin görülme sıklığını ve şiddetini hastaların kişisel özellikleri de etkilemektedir. OM çocuk hastalarda kanser tedavisine ek olarak çok ağrılı ve rahatsız edici olduğundan morbidite oranında artışa sebep olmaktadır.[1] OM 'nin hastaneye yatışı gerektirecek kadar şiddetli, besin alımının, ağız bakımının ve yaşam kalitesinin azalmasına yol açacak kadar da etkili olduğu bilinmektedir.[3] Ayrıca OM'nin hastanın bağışıklığı baskılanmış bir durumda olduğu bir zamanda hastayı ikincil enfeksiyonlara maruz bırakabileceği de bildirilmiştir.[2] Bununla beraber OM'in tedavisinde pek çok yöntem kullanılmaktadır.[6] Çocuklar için oldukça zor bir komplikasyon olan OM'in tedavisinde farmakolojik ve nonfarmakolojik yöntemler uygulanmaktadır.[4] Gargaralar, jel ve sprey şeklindeki analjezikler, kortikosteroidler farmakolojik tedavi sürecinde kullanılan ajanları oluşturmaktadır.[7] Nonfarmakolojik tedavi yaklaşımları arasında ise soğuk uygulama, tuzlu su gargarası, topikal bal uygulaması, ılık kafeinsiz içecekler ve zeytinyağı bulunmaktadır.[1,2] Oral mukozitin olumsuz sonuçlarını en aza indirmede ve etkili yönetiminde hemşirelere oldukça önemli görevler düşmektedir. Yapılan bu sistematik incelemede, 0-18 yaş aralığında kanser tedavisi gören çocuklarda gelişen OM yönetiminde kullanılan hemşirelik bakım uygulamalarını güncel ve kanıt düzeyi yüksek bilgiler ışığında literatüre katkısını incelemek amaçlanmıştır.

GEREÇ VE YÖNTEM

Araştırmanın Türü

Araştırma bir sistematik derlemedir.

Araştırma Sorusu

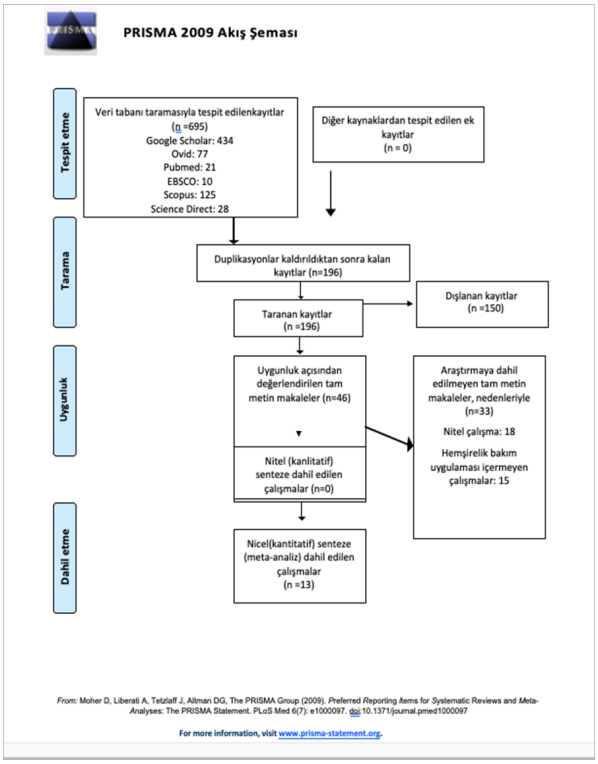
Oral mukozitin yönetiminde kullanılan güncel hemşirelik yaklaşımları nelerdir?

Dâhil Edilme ve Dışlanma Kriterleri

Kanser tedavisi gören çocuklarda OM yönetimi konusunda hemşirelik uygulamalarına dairkanıt düzeyleri seviye I ile seviye II olan, dili İngilizce ve tam metin olarak ulaşılan çalışmalar dâhil edilmiştir (N=46). Kanser tedavisi gören çocuklarda OM yönetimi konusunda hemşirelik uygulamaları dışında kalan, dili İngilizce olmayan, 0-18 yaş aralığını içermeyen çalışmalar ile niteliksel çalışmalar ve olgu sunumları araştırma haricinde tutulmuştur (N=33).

Verilerin Toplanması

Bu çalışmada güncel bir bakış ile OM yönetiminde kullanılan hemşirelik bakım uygulamaları ile ilgili bilgiler sunulmuştur. 2019 ile 2022 arasında kanser tedavisi gören 0-18 yaş aralığındaki çocuklarda gelişen OM yönetiminde kullanılan hemşirelik bakım uygulamalarını inceleyen Meta analiz ve RCT'ler geriye doğru incelenmiştir. PubMed, Scopus, Google Scholar, Science Direct, Ovid Medline, EBSCO veri tabanlarında oral mucositis, children, pediatric, managament, cancer, nursing anahtar kelimeleri kullanılarak yapılan taramalarda toplam 695 çalışmaya ulaşılmıştır. Dâhil edilme kriterlerine uyan çalışmalar incelenmiştir (N=46). Bu kapsamda dâhil edilme kriterlerine uymayan çalışmalar araştırma haricinde tutulmuştur (N=33).Araştırma haricinde tutulan tam metin makalelerin 18 tanesi nitel, 15 tanesi ise hemşirelik bakım uygulaması içermeyen çalışmalardır. Toplam 13 tane tam metin olarak ulaşılan, dili İngilizce ve kanıt düzeyleri I-II olan çalışmalar incelenmiştir (Şekil 1). Araştırmaya dâhil edilen çalışmalar araştırma yöntemi, örneklem, yayın tarihi, hemşirelik uygulamaları, kaynak ve sonuçlar açısından değerlendirilmiştir.



Şekil 1. Literatür araştırmasını gösteren akış şeması (PRISMA)

Araştırmanın Etik Boyutu

Araştırmacı tarafından incelenen veri tabanlarında belirlenen kriterlere uyan ve erişimeaçık olan çalışmalar inceleme dâhiline alınmıştır. Araştırma sistematik bir inceleme olarak yapıldığından etik kurul izni gerekmemiştir.

Bias Riski

Araştırmaya dâhil edilen RCT çalışmaların beş tanesinde çift körleme bir tanesinde tek körleme yapılarak bias riski ortadan kaldırılmıştır. Bununla beraber RCT olmayan çalışmaların kalite değerlendirilmesi için Newcastle Ottowa Skalasının (NOS) kullanılması planlanmıştır.

Araştırmanın Sınırlılıkları

Erişime açık olmayan veri tabanlarında inceleme yapılamamıştır. Sadece dili İngilizce olan hakemli dergilerde

yayımlanmış çalışmalar araştırma kapsamına alınmıştır.

BULGULAR

Araştırma kapsamında toplam 13 makale değerlendirilmiştir. Değerlendirilen çalışmaların 7 tanesinin kanıt düzeyi seviye I, 6 tanesinin ise seviye II'dir. Araştırma kapsamında toplam 6 RCT dâhil edilmiştir. Hem RCT'lerin hem de sistematik derlemelerin çalıştıkları çocukların yaş aralığı genel olarak 1-18'dir. OM yönetiminde en çok kullanılan bakım uygulamaları arasında klorheksidin, sodyum bikarbonat, bal ve zeytinyağı gelmektedir. Günümüzde kullanılan ağız bakım solüsyonlarında bulunan sodyum bikarbonatın ve gargaralarda bulunan klorheksidinin OM'yi önlemede ve şiddetini azaltmada diğer yöntemlere göre daha az etkili olduğu saptanmıştır (Tablo 1).

TARTIŞMA

Bu çalışmada temel ağız bakımı, ağrı yönetimi, sekonder enfeksiyonların önlenmesi ve tedavisi ve OM'li pediatrik hastalarda destekleyici bakım dâhil olmak üzere hasta yönetiminin çeşitli alanlarını değerlendirmiştir. Çocuklarda OM'in şiddeti arttıkça ağız bakım protokolüne uyumunun azaldığı saptanmıştır.[4] Bu yüzden şiddetli OM'i olan çocuklar için gerekli olan bakım yükünün arttığını söylemek yanlış olmayacaktır.[11] Bu noktada hemşirelere önemli görev ve sorumlulukların düştüğünü vurgulamak oldukça önem arz etmektedir.[12] Günümüzde temel ağız bakımında klorheksidinli garga-

Tablo 1. Oral mukozit yönetiminde hemşirelik bakım uygulamaları (Kanıt Düzeyi I-II)

Kaynaklar	Örneklem	Yöntem	Sonuçlar	Kanıt düzeyi
Miranda Silva W, Wagner Silva W, Zadik Y, et al. (2020) Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Clinical practice guidelines for the management of mucositis: sub-analysis of current interventions for the management of oral mucositis in pediatric cancer patients[5]	2011-2019 arası 10.195 makale taranmış, 18 yaş altı OM tanısı alan çocukların yer aldığı RCT'ler ve yarı deneysel çalışmalar dâhil edilmiştir. (N=45)	RCT olan çalışmaların Sistematik derlemesi	Yüksek kanıtlı çalışmaların olmamasına rağmen, temel ağız bakımı protokolünün uygulanması da OM'yi engellemede oldukça uygun olarak görülmüştür.	Seviye I
Semerci R, Kocaslan EN. (2022) Effect of chewing gum on the management of chemotherapy-induced oral mucositis in children: Systematic review of experimental studies[8]	2007-2019 arası 32.829 tane makale taranmıştır. 5-18 yaş ve OM yaşayan çocukların yer aldığı RCT ve yarı deneysel çalışmalar dâhil edilmiştir. (N=5)	RCT olan çalışmaların Sistematik derlemesi	Bu sistematik derleme, sakız çiğnemenin hafif ve orta dereceli OM derecesini azalttığını ancak şiddetli OM'yi etkilemediğini ortaya koymuştur.	Seviye I
Hao S, Ji L, Wang Y. (2022) Effect of Honey on Pediatric Radio/Chemotherapy-Induced Oral Mucositis (R/CIOM): A Systematic Review and Meta-Analysis[9]	2016-2020 tarihleri arası 316 makale taranmış ve tam metin analizi için toplam 25 makaledeğerlendirilmiştir. (5-18 yaş arası çocuk)	RCT olan çalışmaların Sistematik derlemesi	Balın pediatrik hastalarda iyileşme süresini, tüm derecelerde oluşumunu önemli ölçüde azaltabileceğini göstermiştir.	Seviye I
Alqahtanı SS, Sıraj Khan DAA. (2022) Management of oral mucositis in children[4]	2005-2021 arası 762 tane makale taranmıştır. 18 yaş altı ve OM yaşayan çocukların yer aldığı RCT dâhil edilmiştir. (N=16)	RCT olan çalışmaların Sistematik derlemesi	Lazer tedavisi, ağız bakım rejimleri, zeytinyağı ve aloe vera gibi yönetimlerin ve glutaminin bir etkisi olduğunu göstermiştir. Zeytinyağının, sodyum karbonata göre daha fazla etkiye sahip olduğu ileri sürülmüştür.	Seviye I
Zhang L, Yin Y, Simons A. Francisco NM, Wen F, Patil S. (2022) Use of Honey in the Management of Chemotherapy-Associated Oral Mucositis in Paediatric Patients[10]	2010-2020 arası 346 tane makale taranmıştır. 1-17 yaş ve OM'li çocukların yer aldığı çalışmalar dâhil edilmiştir. (N=51)	RCT olan ve olmayan çalışmaların Sistematik derlemesi	Balın, kemoterapinin neden olduğu OM için tedavilerden veya tercih edilen önleme seçeneklerinden biri olarak dâhil edilmesi gerektiğini önermiştir.	Seviye I
Ferrández-Pujanteb A, Pérez-Silva A. Serna-Munoz C, et al, (2022) Prevention and Treatment of Oral Complications in Hematologic Childhood Cancer Patients: An Update[3]	114 makale taranmış ve tam metin analizi için toplam 29 makale seçilmiştir. (0-18 yaş arası çocuk)	RCT olmayan çalışmaların Sistematik derlemesi	Erken aşamalardan itibaren önlemeye dayalı standart protokollerin kullanılması, kanser tedavilerinin yan etkilerini ve komplikasyonları en aza indirgemede en etkiliyöntem olarak gösterilmiştir.	Seviye I
Maracajá Bezerra MP, Vieira IT, Dos Santos FG, Arrais Pibeiro IL, De Sousa SA, Gondim Valença AM. (2022) The impact of oral health education on the incidence and severity of oral mucositis in pediatric cancer patients: a systematic review and meta-analysis[11]	2022' ye kadar 1827 makale taranmış ve 1-18 yaş çocuk, 21 makale seçilmiştir.	RCT olmayan çalışmaların Sistematik derlemesi	Ağız sağlığı eğitimi stratejilerinin uygulanmasının takip dönemindeki pediatrik onkoloji hastalarında OM insidansını ve şiddetini azalttığı bulunmuştur.	Seviye I
Konuk Sener D, Aydın M, Cangur S, Güven E. (2019) The Effect of Oral Care with Chlorhexidine, Vitamin E and Honey on Mucositis in Pediatric Intensive Care Patients: A Randomized Controlled Trial[12]	2-18 yaş arası 150 çocuk 6 grup oluşturulmuş her bir grup (N=25).	RCT Klorheksidin E Vitamini Bal	OM yönetiminde en etkili ajanın E vitamini ve ikinci en etkili ajanın bal olduğunu belirlemiştir. Klorheksidinin OM yönetiminde diğer ajanlara göre daha az etkili olduğu gözlenmiştir.	Seviye II
Mubaraki S, Chandra Pani S, Alseraihy A, Abed H, Alkhayal Z. The efficacy of two different oral hygiene regimens on the incidence and severity of oral mucositis in pediatric patients receiving hematopoietic stem cell transplantation: A prospective interventional study[13]	7-10 yaş arası 45 çocuk. 3 grup olarak çalışılmış ve her bir grup (N=15).	RCT Klorheksidin ve sodyum bikarbonat Dişlerini günde 2 kez ekstra yumuşak diş fırçası ile fırçalamak Az miktarda aşırı doymuş kalsiyum oral sprey	Aşırı doymuş kalsiyum fosfat sprey kullanan grupta oral mukozit şiddetinin azalmadığı gözlemlenmiştir. Ayrıca ağız hijyeni rejimine ekstra yumuşak bir diş fırçasının dâhil edilmesinin OM insidansını azaltmadığını ve aslında oral mukozitin şiddetindeki bir artıştan sorumlu olabileceğini göstermiştir.	Seviye II
Hassan H, Kinsey S, Phillips B. (2022) Mucositis reduction with probiotics in children with cancer: a randomised-controlled feasibility study[7]	1-18 yaş arası 34 OM'li çocuğa ulaşılmış. 10 çocuk çalışmaya dâhil edilmiştir.	RCT 1.grup: (n:4) Probiyotik 2.grup: (n:6) Placebo	Probiyotik kullanımının OM yönetiminde etkili bir tedavi olarak kullanımı için daha fazla ve yeterli sayıda RCT çalışmalar ile kanıtlanması gerektiği sonucuna ulaşılmıştır.	Seviye II
Alkhouli M, Laflour M, Alhaddad M. (2020) Efficacy of Aloe-Vera Use for Prevention of Chemotherapy-Induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia: A Randomized Controlled Clinical Trial[14]	3-6 yaş aralığı 26 çocuk	RCT. 1.grup (n:13) Aloe-vera 2.grup (n:13) sodyum bikarbonat	Gözlenen bulgulara göre, aloe-vera grubunda OM dereceleri sodyum bikarbonat grubuna göre daha az şiddetliydi. Aloe-vera solüsyonunun topikal uygulamasının çocuklarda OM'un önlenmesinde etkili olduğunu göstermiştir.	Seviye II
Widjaja NA, Pratama A, Prihaningtyas R, Irawan R, Ugrasena I. (2020) Efficacy Oral Glutamine to Prevent Oral Mucositis and Reduce Hospital Costs During Chemotherapy in Children with Acute Lymphoblastic Leukemia[15]	1-18 yaş arası 48 çocuk	RCT. 1.grup (n:24) Glutamin 2.grup (n:24) Plasebo	Plaseboya karşı oral glutamin ile oral mukozitin önlenmesinde anlamlı bir fark vardı. Bu çalışma, glutaminin, yüksek doz kemoterapi alan çocuklarda oral mukozit insidansını ve şiddetini azaltabileceğini ileri sürülmüştür.	Seviye II
Singh R, Sharma S, Kaur S, Medhi B, Trehan A. (2019) Effectiveness of topical application of honey on oral mucosa of children for the management of oral mucositis associated with chemotherapy[16]	2-18 yaş aralığı 100 çocuk	RCT. 1.grup (n:50) Topikal bal uygulaması 2.grup (n:50) Rutin analjezik ve antiseptik jel uygulaması	Balın oral mukozaya topikal olarak uygulanmasının, kemoterapinin neden olduğu oral mukozitin ciddiyetini ve süresini azaltmada etkili olduğu görülmüştür.	Seviye II

raların ve sodyum bikarbonatın kullanıldığı görülmüştür. Bununla birlikte yapılan deneysel çalışmalarda temel ağız bakım solüsyonlarının OM engellemede ve şiddetini azaltmada diğer yöntemlerle etkinliği karşılaştırılmıştır.[12-14,16] Konuk Sener ve ark. yaptığı çalışmada E vitamini, bal ve klorheksidinin OM tedavisinde etkinliği araştırılmıştır. Klorheksidinin OM yönetiminde diğer ajanlara göre daha az etkili olduğu gözlenmiştir.[12] Benzer şekilde Alkhouli ve ark. yaptığı bir çalışmada aloe veranın OM'in yönetiminde sodyum bikarbonata göre etkinliği değerlendirilmiştir. Gözlenen bulgulara göre, aloe-vera grubunda OM şiddetinin dereceleri sodyum bikarbonat grubuna göre daha hafif seyretmiştir.[14] Widjaja ve ark. yapmış olduğu bir çalışmada OM'in şiddetini azaltmada oral glutamin kullanımının rutin kullanılan ağız bakımı solüsyonlarına göre etkinliğini değerlendirmiştir.[15] Plaseboya karşı oral glutamin ile OM'in önlenmesinde anlamlı bir fark tespit edilmiştir. Bu çalışma glutaminin, yüksek doz metotreksat kemoterapisialan çocuklarda oral mukozit insidansını ve şiddetini azaltabileceğini ileri sürmüştür.[15] Bu bilgiler ışığında OM'in önlenmesinde ve tedavisinde klorheksidin ve sodyum bikarbonatın etkinliğinin diğer yöntemlere göre daha az etkili olduğunu söylemek mümkündür.

OM'in yönetiminde balın kullanımının etkinliğini ölçmek için pek çok araştırma yapılmıştır. Hao ve ark. yapmış olduğu sistematik bir incelemede balın pediatrik hastalarda iyileşme süresini ve tüm derecelerde oluşumunu önemli ölçüde azaltarak etkileyebileceğini göstermiştir.[9] Benzer şekilde Zhang ve ark. yaptığı bir çalışmada balı kemoterapinin neden olduğu OM'in tedavilerden veya tercih edilen önleme seçeneklerinden biri olarak dâhil edilmesi gerektiğini önermiştir.[10] Singh ve ark. yapmış olduğu çalışmada balın oral mukozaya topikal olarak uygulanmasının kemoterapinin neden olduğu OM'nin ciddiyetini ve süresini azaltmada rutin analjezik ve antiseptik jel uygulamasına göre daha etkili olduğunu göstermiştir.[16] Yapılan çalışmalar ışığında çocuklarda bal kullanımının OM yönetiminde etkili olduğu söylenebilir.

Bununla berber OM'in önlenmesi ve tedavisinde probiyotik kullanımının ve sakız çiğnemenin etkinliği ile ilgili tartışmalar devam etmektedir.[5,7,8] Probiyotik kullanımının OM yönetimde etkinliğini kesin olarak gösteren çalışmalar yetersiz olmakla beraber sakız çiğnemenin hafif ve orta dereceli OM derecesini azalttığını, ancak şiddetli OM'yi etkilemediğini ortaya süren çalışmalar bulunmaktadır.[7,8]

Pediatrik hastaların OM varlığında diş fırçalama sırasında rahatsızlık duydukları tespit edilmiştir.[4,5] Bunun da OM'in irritasyonundan kaynaklı ağrı duyularının artmasıyla ilişkili olduğu düşünülmektedir. Mubaraki ve ark. yapmış olduğu çalışmada, ağız hijyeni rejimine ekstra yumuşak bir diş fırçasının dâhil edilmesinin oral mukozit insidansını önemli ölçüde azaltmadığı belirlenmiş ve hatta oral mukozit şiddetindeki artıştan sorumlu olabileceği düşünülmüştür.[13]

SONUÇ

Oral mukozit kemoterapi ve radyoterapi alan çocuk hastalarda yaşam kalitesini düşüren önemli bir komplikasyon olarak karşımıza çıkmaktadır. Oral mukozitin tedavisinde balın ne kadar önemli bir yere sahip olduğu çalışmalarla gözler önüne konulmuştur. Bununla birlikte E vitamini desteğinin baldan daha etkili olduğu gösterilmiştir. Yine oral mukozitin yönetiminde zeytinyağı ve aloe-veranın etkinliği çalışmalarla kanıtlanmış ve topikal zeytinyağı uygulamasının alana entegre edilmesi gerektiği önerilmiştir. Ağız bakımında kullanılan sodyum bikarbonatın ve klorheksidinin OM'yi önlemede ve şiddetini azaltmada diğer yöntemlere göre daha az etkili olduğu saptanmıştır. Araştırmalar göstermektedir ki; oral mukozitin gelişimini önleme en önemli yönetim stratejilerimizden biri olmalıdır. Bu süreçte diğer etkili olan ajanlar; E vitamini, zeytinyağı, bal, glutamin, aloe vera, orta ve az şiddetli OM'de sakız çiğnemek olarak gösterilebilir. Oral mukozitin yönetiminde hemşirelik bakım uygulamaları olarak yapılabilecek pek çok girişim bulunmaktadır. Bu yüzden hemşireler randomize kontrollü çalışmalar yaparak daha fazla kanıtlar sağlamalı ve çocuklar için çok önemli bir sorun olan oral mukozitin yönetimi için alternatif yollar üretmelidir.

Etik Kurul Onayı: Çalışma metodolojisinden dolayı gerek görülmemiştir.
Bilgilendirilmiş Onam: Çalışma metodolojisinden dolayı gerek görülmemiştir.
Hakem Değerlendirilmesi: Dış bağımsız
Yazar Katkıları: Fikir/ET; Tasarım/ET, GA, TK; Denetleme/TK, FGT; Kaynaklar/ET; Veri Toplama/ET, GA; Literatür Taraması/ET, GA; Eleştirel İnceleme/TK, FGT.
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Ethics Committee Approval: It was not deemed necessary due to the study methodology.
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FİZİKSEL AKTİVİTE DANIŞMANLIĞINDA YENİ BİR BAKIŞ AÇISI: "SNACKTIVITY"
A NEW PERSPECTIVE IN PHYSICAL ACTIVITY COUNSELING: "SNACKTIVITY"

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ÖZ

Fiziksel aktivite danışmanlığında bireylerin hedeflenen fiziksel aktivite seviyelerine ulaşabilmeleri için kalıcı davranış değişikliğine ihtiyaçları vardır. Bireylerde davranış değişikliği oluşturmak için gerçekçi, uygulanabilir hedefler belirlemek önemlidir. Aktivite atıştırmalığı olarak da bilinen "Snacktivity" yaklaşımı fiziksel aktivite davranışında küçük farklılıklar sağlayarak kalıcı değişiklikleri hedefler. Ayrıca bu yaklaşım günlük hayata uyarlanabilen basit, kısa süreli aktivitelerle sedanter davranışın ve aktivite bariyerlerinin engellenmesine yardımcı olur. Uygun yer, zaman ve ekipman olmadığı için egzersiz yapamadığını ifade eden sedanter bireylerde hiç fiziksel aktivite yapamamaktansa küçük aktivite sürelerinin birleştirilmesi yoluyla hedeflenen fiziksel aktivite seviyesine ulaşılması sağlanır. Toplumda fiziksel aktivite düzeyinin arttırılmasının önemli bir halk sağlığı politikası olduğu düşünüldüğünde "Snacktivity" yaklaşımı kayda değer bir konudur. Bu derleme "Snacktivity" yaklaşımının fiziksel aktivite danışmanlığındaki rolüne odaklanarak farkındalık oluşturmayı hedeflemektedir.

Anahtar kelimeler: danışmanlık, fiziksel uygunluk, sedanter davranış, transteorik model.

ABSTRACT

Individuals need permanent behavioral changes in physical activity counseling to reach targeted physical activity levels.Determining reasonable and applicable goals for creating behavior change in individuals is critical. The "Snacktivity" approach, also known as "activity snacks", targets permanent changes by providing small modifications in physical activity behavior. In addition, this approach helps to prevent sedentary behavior and activity barriers by using simple, short-term activities that can be adapted to daily life. The targeted activity is achieved by accumulating small activity snacks rather than being unable to do any activity in sedentary individuals who state they cannot do activities due to the lack of appropriate place, time, and equipment.Considering that increasing physical activity levels in the community is an important public health policy, the "Snacktivity" approach is a notable issue. This review aims to raise awareness by focusing on the role of the "Snacktivity" approach in physical activity counseling.

Keywords: counseling, physical fitness, sedentary behavior, transtheoretical model.

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GİRİŞ

Fiziksel inaktivitenin başlıca kardiyovasküler, kas-iskelet, solunum ve immün sistem problemlerini ve mortalite riskini arttırdığı düşünüldüğünde fiziksel aktivite danışmanlığı bu risklerin azaltılmasında önemlidir.[1] Fiziksel aktivite danışmanlığında bireyleri aktiviteye teşvik etmek, bireylerin aktivite yapmasını kolaylaştırıcı etkenleri ve bariyerleri belirlemek, bu yönde bireyselleştirilmiş danışmanlık programlarını motivasyonel görüşmeler yoluyla uygulamak tavsiye edilir.[2]Güncel çalışmalarda aktivite danışmanlığında "Snacktivity" yaklaşımı vurgulanmaktadır. "Activity" ve "Snacks" kelimelerinin birleşimi olan "Snacktivity" yaklaşımında, "Aktivite atıştırmalıkları" olarak ifade edilen 2-5 dakika süren kısa süreli aktivitelerin birleştirilmesi yoluyla bireylere aktivite alışkanlığı kazandırmak hedeflenir.[3]

Fiziksel Aktivite Danışmanlığında Davranış Değişim Teorileri ve Bariyerler

Fiziksel aktivite danışmanlığı bireylerde aktivite farkındalığı ve davranış değişikliği oluşturmak için bireyleri dinleme, anlama, fiziksel aktivite konusunda bilinçlendirme, aktivite kolaylaştırıcılarını ve bariyerlerini belirleme, kısa ve uzun dönem hedefler planlamayı kapsar.[4] Fiziksel aktiviteyi artırmak bir davranış değişim sürecini içerir. Bireylerin fiziksel aktiviteye katılımlarını arttırmak için 'hareket et' tavsiyesi yerine, aktiviteye katılımlarını arttıracak yaklaşım ve yöntemlerin geliştirilmesi gerekir. Davranışı şekillendiren ve davranış değişikliği sağlamada işe yarayan faktörleri belirlemede büyük ilerleme kaydedilmiş olsa da bireysel davranışsal eylemler ve sonuçlar farklılıklar içerdiğinden, mevcut halk sağlığı politikaları toplum sağlığında önemli ilerlemeler sağlamak için bireysel davranışlardaki küçük, kümülatif değişikliklerin önemini vurgulamaktadır.[5]

Davranış değişikliği oluşturmada kullanılan "Sağlık İnanç Modeli", "Sosyal Bilişsel Teori", "Mantıklı Eylem Teorisi", "Kişilerarası Davranış Teorisi", "Planlı Davranış Teorisi" gibi teorilerin yanı sıra son zamanlarda en sık kullanılan yöntem Transteorik Model'dir. Transteorik Model'e göre değişim aşamaları düşünme öncesi aşama, düşünme aşaması, hazırlık aşaması, eylem aşaması ve sürdürme/devam ettirme aşamalarından oluşur. Transteorik Model, bireylerin önümüzdeki 6 ay içerisinde hedeflenen davranış değişikliğini yapmayı düşünmediği aşamadan, davranış değişikliğini 6 ay boyunca düzenli olarak sürdürdüğü aşamaya kadar olan süreçleri içerir. Bu model sadece davranışa değil davranışsal niyete de odaklanmaktadır.[6] Bu yüzden fiziksel aktivite danışmanlığında davranış değişikliği oluşturmak için, öncesinde davranışı etkileyen bireysel bariyerlerin ve kolaylaştırıcıların belirlenmesi, günlük yaşam aktivitelerinin sorgulanması, kişiye özel ve bireylerin rutinlerine uyarlanmış aktivite tavsiyeleri belirlemek önemlidir.[2] Her bireyde farklılık göstermesine rağmen en yaygın bariyerler zaman kısıtlılığı, motivasyon kaybı, yorgunluk, aktivite yapmayı eğlenceli bulmama, düşme korkusu, aktiviteyi güvenli bulmama, eşlik edecek birini bulamama gibi kişisel faktörler ve hava durumu, trafik, aktivite yapmak için alanın olmaması gibi çevresel faktörlerdir.[2,7,8]

Bariyerlerin Önlenmesinde ve Davranış Değişikliğinde "Snacktivity" Yaklaşımının Önemi

Fiziksel aktivitenin 10 dakika ve daha uzun sürelerde yapılması gerekliliğini vurgulayan 2020 ve öncesi rehberler güncellenerek fiziksel aktivite davranışında küçük değişiklikler yapmanın hiç yapmamaktan daha anlamlı olduğu vurgulanmıştır.[9,10] Ayrıca güncel rehberde, zorunlu olarak oturma süresi fazla olan bireyler de (tekerlekli sandalye kullanıcıları gibi) göz önünde bulundurularak oturma süresi yerine sedanter davranış terimi kullanmanın daha uygun olacağı görüşü vurgulanarak hareketsiz kalınan sedanter zamanların hafif şiddette bile olsa bir aktiviteyle yer değiştirmesi gerekliliği üzerinde durulmaktadır.[9] Bu sebeple "Snacktivity" yaklaşımı ile günde beş dakika süren altı aktivite atıştırması bile bireyin aktivite alışkanlığı kazanmasına katkı sağlamaktadır.[8] Özellikle temel fiziksel aktivite bariyeri zaman kısıtlılığı olan bireylerde, haftalık 150-300 dakika orta veya şiddetli fiziksel aktivite sürelerine ulaşmak planlama veya çok fazla bilişsel ve fiziksel çaba gerektirirken, beceri, ekipman, kıyafet değişikliği bile gerektirmeden yapılabilen, daha az planlama ve çaba gerektiren "Snacktivity" yaklaşımı ile günlük yaşama kolayca dahil edilebilen basit aktiviteler bu bariyerle baş etmeyi kolaylaştırabilir. Küçük değişiklikleri başlatmak ve sürdürmek çok daha kolay olduğundan "Snacktivity" yaklaşımı ile etkili bir davranış değiştirme tekniği kullanılmış olur.[8,11] Bu şekilde bireylerin niyetlerini eyleme dönüştürmeleri desteklenebilmektedir.[3]Küçük değişiklikleri başarmak bireylerin görev ve düzenleme özyeterliliğini, alışkanlık oluşturma becerisini geliştirir. "Snacktivity" yaklaşımı aktif olmayan bireylerin güvenlerini geliştirmeye yardımcıdır. Ayrıca aktivite katılımı az olan ve katılım konusunda bariyerleri fazla olan yaşlı, kronik hastalığı olan veya engelli bireylerde de uygun bir yaklaşımdır.[8] Günlük yaşamda sık yapılan bazı rutinlerin içine fiziksel aktivite eklemek bireylerin aktivite bariyerlerinin de önüne geçmektedir. Telefonla konuşurken bir taraftan yürümek, dişleri fırçalarken bacak hareketleri yapmak sık yapılan rutinlere aktivite ekleme örneklerindendir. Bu yönüyle "aktivite atıştırmalıkları" ek bir süre gerektirmeden aktivite yapmaya imkan sağlar.[3,8] "Snacktivity" yaklaşımı ile ilgili diğer örnek aktivite atıştırmalıkları Tablo 1.'de verilmiştir.[3]

"Snacktivity" Yaklaşımının Sağlıkla İlişkili Faydaları

Fiziksel aktivite rehberlerinin haftanın en az iki gününün kas kuvvetini arttırmaya yönelik aktivitelerden oluşması gerekliliği önerisi, özellikle düşme, osteoporoz ve kırık risklerinin azaltılmasında kayda değerdir.[9] Ancak yetişkinlerin çok azı (yaklaşık %20) bu hedefi başarabilmektedir.[12] "Snacktivity" yaklaşımı kas kuvvetlendirme aktivitelerinin birçoğunu yapmaya olanak tanır. Örneğin mutfakta su ısıtıcısı çalışırken çömelip kalkmak gibi bir aktivite kısa süreli, pratik ve ekipman ihtiyacına gerek olmadan yapılabilir.[8] Ayrıca bu yaklaşım gün boyunca uzun süreli sedanter davranıştan korunmada etkindir. Böylelikle hareketsiz davranış döngüsünün kırılmasıyla bireylerde kardiyo-metabolik hastalık riskinin azalmasında kısa süreli aktivitelerin de önemi olduğu hipotezi güçlenmektedir.[13] "Snacktivity" kavramının literatürde yeni yer alması sebebiyle konuyla ilişkili az sayıda çalışma bulunmaktadır.[3,8,14-18] Kısıtlı sayıda çalışma küçük fiziksel aktivite sürelerinin biriktirilmesinin sağlığa önemli faydaları olduğunu göstermektedir. Boreham ve arkadaşları kısa süreli merdiven çıkma aktivitelerinin genç sedanter kadınlarda maksimal oksijen tüketiminde %17,1 artışı, düşük yoğunluklu

Tablo 1. "Snacktivity" yaklaşımına göre aktivite örnekleri

İşte yapılabilecek aktiviteler
Otururken kol hareketleri
Arabayı biraz daha uzağa park edip yürümek
Daha uzaktaki/başka kattaki tuvaleti kullanmak
İş arkadaşlarıyla görüşmeler yaparken aynı anda yürümek
Arama yaparken masadan uzaklaşmak ve yürümek
Öğle yemeği arasında tempolu yürümek
Asansör veya yürüyen merdivenleri kullanmak yerine merdivenlerden çıkmak/inmek
Arkadaşlarla iletişim için telefon/elektronik posta kullanmak yerine arkadaşın yanına yürümek
İşte "lunge", "squat" gibi egzersizler yapmak
Otobüsten bir durak önce inip yürümek
Evde ve boş zamanda yapılabilecek aktiviteler
Merdivenleri birkaç kez inip çıkmak
Ev işleri
Telefonla konuşurken yürümek
Bulaşıkları yıkarken ayak parmakları üzerinde yükselip inmek
Su ısıtıcısının kaynamasını beklerken hareket etmek
Yerinde adım almak
Bahçe işleri
Dişleri fırçalarken çömelip kalkmak (squat)
Merdivenleri kullanarak şınav (press up) yapmak
Evi süpürürken "lunge" yapmak
Alışveriş yaparken alışveriş arabası yerine sepet kullanmak
Yakın mağazalara giderken yürümek/koşmak/bisiklete binmek
Otururken teneke/şişe ile kolları büküp açmak (biceps curl)
Oturma odasında/mutfaktayken dans etmek
Yakındaki park etrafında tempolu yürümek
Tempolu yürüyüşü arttırmak için köpek ile birlikte yürümek
Çocuklarla parkta oynamak
Atlamak/İp atlamak
Araba yıkamak
Çocukları okuldan almak/bırakmak için yürümek

lipoprotein kolesterol düzeyinde ise %7,7 azalmayı sağladığını bulmuşlardır.[19] Stenling ve arkadaşları optimal minimum bir aktivite süresi belirleyememekle birlikte her biri birer dakikalık üç kez merdiven çıkma aktivitesinin genel ruh halinde olumlu artışa katkı sağladığını vurgulamışlardır.[20] Kısa süreli aktivite sürelerinin yetişkinlerde sağlıkla ilişkili yararlar ile stres ve depresif belirtilerin azalması ve benlik saygısının artmasına katkı sağladığını belirten çalışmalar bulunmaktadır.[21,22] Yaşlı bireylerde "Snacktivity" yaklaşımının etkinliğini inceleyen güncel bir derlemede, bu yaklaşımın özellikle huzur evleri ve uzun süreli bakım evlerinde kalan yaşlı yetişkinlerin aktiviteden keyif alma, aktivite yapmaya olan motivasyonlarını arttırma ve işlevsel kapasitelerini geliştirmede etkili olduğunu ve bu tesislerde daha fazla kullanılması gerekliliğini vurgulamışlardır.[17] Murphy ve arkadaşları ise aynı toplam sürede olan sürekli yapılan veya biriktirilmiş fiziksel aktivitenin kardiyovasküler uygunlukta benzer gelişmeler sağladığını raporlamışlardır.[23] Güncel bir derleme aktivite atıştırmalıklarının ölüm oranı, kardiyovasküler hastalık ve kanser riskini azaltmada önemli boyutlarda etkili, uygulanabilir, iyi takip edilebilir ve güvenli olduğunu belirtirken, kronik hastalığı olan ve yaşlı olan bireylerde sağlığı iyileştirme üzerine etkilerinin henüz belirsiz olduğuna dikkat çeker.[18] "Snacktivity" yaklaşımının sağlıklı ve kronik hastalığı olan bireylerde fonksiyonel kapasite ve yaşam kalitesine etkileri ile ilgili daha fazla çalışmaya ihtiyaç vardır.

Katılımcıların "Snacktivity" Yaklaşımına Bakış Açısı

İnsanlara aktivite hakkında basit bilgi vermek kalıcı davranış değişikliğine yol açmaz. Çeşitli teknolojiler geliştirilse de önemi yeni artan yaklaşımla ilgili halkı bilgilendirmek ve kalıcı davranış değişikliği oluşturmak için ek stratejiler gereklidir.[8]

Haftalık, düzenli, orta-şiddetli fiziksel aktivite tavsiyesini karşılayamayan sedanter bireylerle yapılan bir çalışmada, bireylere yarı yapılandırılmış özellikte aktivite danışmanlığı programı uygulanmış ve aktivite atıştırmalıklarını içeren broşür hazırlanarak verilmiştir. Çalışma sonrası "Snacktivity" ile ilgili görüşleri alınan katılımcılar, aktivite atıştırmalıklarının daha kolay olduğu için başarma hissi sağladığını ve bu kısa süren aktiviteleri biriktirerek haftalık 150 dakikalık orta-şiddetli aktivite hedefine ulaşmaları gerektiğini anladıklarını ifade etmişlerdir. Katılımcıların yaklaşık yarısı "Snacktivity"nin bireysel koşullara uyarlanabildiğini, her yaştan ve farklı fiziksel uygunluk seviyelerindeki bireylere uygun, hedeflenen aktivite seviyesine ulaşmada başarılı bir yaklaşım olduğunu belirtmişlerdir. Katılımcıların bazıları aktivite atıştırmalıklarının günün herhangi bir saatinde tamamlanabileceğini, herhangi bir özel ekipman ve kıyafete ihtiyaç duyulmadan yapılabileceğini ve tüm bunların günlük yaşamlarına rahatlıkla uyarlanabileceğini belirtmişlerdir. Öte yandan bu yaklaşımla ilgili bireylerin olumlu geri bildirimleri olsa da kısa süreli aktivitele-

rin birleştirilmesinin yeterli olamayabileceği, unutulabileceği riski de vurgulanmaktadır.[3] Krouwel ve arkadaşları ise fiziksel olarak aktif olmayan yetişkin bireylerde 3 hafta boyunca günlük hayatlarına dahil edebilecekleri "Snacktivity" müdahalesini, aktivite monitörü ve aktivitelerin izlenebileceği mobil uygulama kullanarak uygulamışlardır. Müdahale sonrası bireyler "Snacktivity" yaklaşımının etkisini değerlendirmişler ve bazı aktivite atıştırmalıklarının geleneksel egzersizlere göre daha uygulanabilir olduğunu, fakat başkalarının yanında bu aktiviteleri yapmakta zorluk yaşadıklarını belirtmişlerdir. Ayrıca katılımcılar mobil uygulama sayesinde kendilerine anlık gelen bildirimlerin davranış değişikliği oluşturmalarını kolaylaştırdığını vurgulamışlardır. Teknoloji kullanımı ile ilgili yaşanan bazı problemler ise bireylerin motivasyonlarını etkileyen önemli bir bariyer olmuştur.[15] "Snacktivity" yaklaşımının önündeki bariyerlerin kaldırılabilmesi ve var olan problemlerin belirlenmesi için daha fazla çalışmaya ihtiyaç vardır.[16]

SONUÇ

Fiziksel aktivite danışmanlığında yeni bir bakış açısı olan "Snacktivity", özellikle aktivite bariyerleri fazla olan ve bu bariyerleri aşmakta zorlanan sedanter bireylerde günlük hayata uyarlanabilen basit, kısa aktivite atıştırmalıklarını içeren bir yaklaşımdır. Halkı fiziksel inaktivite konusunda bilgilendiren ve aktivite yapmaya teşvik eden bilgilendirme yazısı ve broşürlerin çoğu, belirli fiziksel aktivite sürelerine tek seferde ulaşmayı hedefler. Fakat çok az kişi gerekli fiziksel aktivite tavsiyelerine uymaktadır. Bireylerin çoğu için uzun, ulaşılamaz, vakit aldığını söyledikleri bu hedefler, aktivite atıştırmalıkları olarak verilen kısa aktivitelerin biriktirilmesi yoluyla daha ulaşılabilir, daha gerçekçi hedefler haline gelebilir. Bu nedenle toplumda fiziksel aktiviteyi arttırmak için kalıcı davranış değişikliği oluşturmak hedeflenmeli, bunun için de basit ulaşılabilir hedefler belirlenmeli ve bu hedeflerin gerçekleştirilip gerçekleştirilemediği takip edilmelidir. "Snacktivity", bireylerin aktivite için ekipman, yer ve zaman bulamadıklarında bile aktivite yapmaya olanak sağlayan bir yaklaşımdır. Bu yaklaşımın bireylerin aktivite zamanlarına, günlük yaşamlarına, aktivite bariyerlerine etkisini kısa ve uzun dönemde inceleyen çalışmalara ihtiyaç vardır.

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Erciyes Üniversitesi Sağlık Bilimleri Dergisi Yayın Kuralları ve Genel Bilgiler

Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü yayını olan Sağlık Bilimleri Dergisi yılda üç defa olmak üzere dört ayda bir yayınlanır. Tıbbın çeşitli dallarındaki klinik ve deneysel araştırma yazıları, orijinal olgu sunumları ve literatür derlemeleri daha önce herhangi bir yerde yayınlanmamış ve yayın için başka bir dergiye gönderilmemiş olmak koşuluyla kabul edilir. Araştırma makalelerinin yayınlanabilmesi için projelerinin ilgili kurumun etik kurulunca onaylanmış olduğu ve insanla yapılan çalışmalarda, çalışma öncesinde hasta ya da gönüllülere bilgilendirme yapılıp onay alındığı belirtilmelidir.

Dergide yazılar Türkçe ve İngilizce olarak yayınlanır. Türkçe yazılarda Türk dilinin bütünlüğü korunmalı, İngilizce yazılar anlaşılır ve hatasız olmalıdır. Yazılar dört örnek (biri orijinal, diğerleri fotokopi) olarak editöre gönderilmeli veya şahsen teslim edilmelidir. Gönderilen yazı ve resimlerin kaybından editörlük sorumlu tutulamaz. Gönderilen yazılar yayınlansın veya yayınlanmasın iade edilmez, yalnız yayınlanmayan resimler veya şekiller istek üzerine yazarına gönderilebilir. Gönderilen yazıların dergi kurallarına göre düzenlenmiş ve basıma hazır hale getirilmiş olması gerekir. Yazıların yayınlanmasındaki gecikmenin en önemli nedeni makalelerin yazım kurallarına göre hazırlanmamasıdır. Yayın kurulu yazım kurallarına uymayan yazıları yayınlamamak, düzeltmek üzere yazara iade etmek yada şekil açısından yeniden düzenlemek yetkisindedir. Yazılarda savunulan fikirlerin sorumluluğu yazara aittir. Yayınlanan yazıların telif hakkı dergiye ait olup derginin izni olmadan kısmen de olsa aktarılamaz.

Editöre çeşitli konularda ve dergide yayınlanan yazılarla ilgili mektuplar yazılabilir ve yazarlarından cevaplandırması istenebilir. Bunların dergide yayınlanıp-yayınlanmaması editörün yetkisindedir. Ayrıca dergide tıp alanındaki ulusal veya uluslararası bilimsel toplantıların tarihi, konusu ve konuşmacıları duyurulmak amacı ile yayınlanır.

Yazım Kuralları

Dergide yayınlanmak üzere editöre gönderilen yazılar A4 kağıdının bir yüzüne 12 punto, çift aralıkla ve kenarlarda üçer cm boşluk bırakılarak yazılmalıdır. Tablo, şekil ve resim yazıları 10 punto ve bir aralıkla yazılmalıdır. Kullanılan kısaltmalar yazı içerisindeki ilk geçtikleri yerde, parantez içinde, açık olarak yazılmalı, özel kısaltmalar yapılmamalıdır. Yazı içindeki 1-10 arası rakamsal veriler yazıyla, 10 ve üstü rakamlarla belirtilmelidir. Ancak, cümle başındaki sayılar yazıyla yazılmalıdır. Şekil ve resimler metin içinde geçiş sırasına göre numaralandırılmalıdır. Araştırma makaleleri ve derlemeler metin, şekil, tablo, kaynaklar dahil 10, olgu sunumları beş daktilo sayfasını geçmemelidir. Yazılar aşağıda belirtilen sıra izlenerek düzenlenmelidir.

Orijinal makalelerde başlık sayfası, özet, giriş, gereç ve yöntem, bulgular, tartışma, kaynaklar; olgu sunumlarında özet, giriş, olgu(ların) sunumu, tartışma ve kaynaklar bölümleri yer almalıdır.

Araştırmaya veya makalenin hazırlanmasına katkıda bulunanlara "teşekkür" varsa tartışma bölümünden sonra yer almalıdır.

Başlık sayfası : Makalenin başlığını, yazarlarının adlarını ve görevlerini (akademik ünvanlarını), hangi kuruluştan gönderildiğini, varsa çalışmayı destekleyen kurumun adını içermelidir. Yazı herhangi bir kongrede tebliğ edilmişse yeri ve tarihi belirtilmelidir. Ayrıca bu sayfada yazışma yapılacak yazarın adı, soyadı, iş ve ev adresleri, telefon ve fax numaraları açıkça yazılmalıdır.

Özet : Ayrı bir kağıda Türkçe ve İngilizce olarak hazırlanmalı başlıklar dahil her biri 250 kelimeyi aşmamalıdır. Özet makaleyi yansıtacak nitelikte olmalı, önemli sonuçlar verilmeli ve bunların yorumu yapılmalıdır. Özette açıklanmayan kısaltmalar kullanılmamalı, kaynak gösterilmemelidir. Özet sayfası yazar adlarını ve adreslerini içermemelidir.

Anahtar kelimeler: Özetten hemen sonra aynı dilde olmak üzere makale ile ilgili en az üç, en fazla beş anahtar kelime verilmelidir. Anahtar kelimelerinin Türkiye Bilim Terimleri'nden (Türkiye Bilim Terimleri); MeSH (Medical Subject Headings) terimlerinin, Türkçe karşılıklarını içeren anahtar kelimeler dizininden seçilmeli ve aşağıda web adresinden kontrol edilmelidir. (bkz: http:// www.bilimterimleri.com)

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Kaynaklar: Sağlık Bilimleri Dergisi, **kaynak gösterim şekli olarak AMA standartlarını kabul etmektedir.** AMA standartlarıyla ilgili detaylı bilgiye https://www.bcit.ca/files/library/pdf/bcit-ama_citation_guide.pdf adresinden ulaşılabilir. Çalışmalar (makale, derleme ve olgu sunumu) için kaynak sayısı 45'i geçmemelidir. **Kaynaklar son 10 yılı içeren literatürü kapsayacak şekilde hazırlanmalıdır.**

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Kaynakların yazımı için örnekler (Noktalama işaretlerine lütfen dikkat ediniz):

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Bir ila Altı Yazar

Author AA, Author BB, Author CC. Title of article. Abbreviated Journal Title. Year; Volume(Issue): Page-Page.doi. Watts T. Initiatingend-of-life carepath ways: A discussionpaper. *J Adv Nursing*. 2012;68(10):2359-2370. doi:xx.xxxx/xxxxxxxxxxxxxx.

Yedi veya Daha Fazla Yazar

Author AA, Author BB, Author CC, et al. Title of article. Abbreviated Journal Title. Year; Volume (Issue): Page-Page.

Bond AE, Eshah NF, Bani-Khalid M, et al. Who uses nursing theory? A univariated escriptive analysis of five years' research articles. *Scand J Caring Sci*. 2011;25(2):404-409. doi:xx.xxxx/xxxxxxxxxxxxxx.

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Davidson Baer E. Keyideas in nursing's first century. *Am J Nursing*. 2012;112(5):48- 55. http://journals.lww.com/ajnonline/Abstract/2012/05000/Key_Ideas_in_Nursing_s_First_Century.27.aspx Published May 2012. Accessed September 23, 2012.

KİTAP İÇİN;

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Tek Yazarlı

Author AA. Title of Work. Location: Publisher; Year: Page-Page.

Saver, Cynthia. *Anatomy of Writing for Publication for Nurses.* Indianapolis, IN: Sigma Theta Tau International; c2011:31-33.

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Author AA, Author BB. Title of Work. Location: Publisher; Year: Page-Page.

Doane GH, Varcoe C. *Family Nursing as Relational Inquiry: Developing Health–Promoting Practice.* Philadelphia, PA: Lippincott Williams &Wilkins; c2005:25-28.

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RAPOR, KONGRE VB İÇİN;

Çevrimiçi Rapor

Author AA. Title of Report. URL. Published/Updated/Revised date. Accessed date. International Monetary Fund. World economic out look update. http://www.imf.org/ external/pubs/ft/weo/2012/update/02/. PublishedJuly 16, 2012. Accessed September 19, 2012.

Konferans Makalesi veya Bildirileri

Presenter AA. Title of paper or presentation. Paperor Poster presented at: Conference Title; Month Day, Year; Location. URL. Accessed date. Cronin C. Memoing: An activetool in research. Poster presented at: RCN Annual International Nursing Research Conference; April 23, 2012. London, UK. http://www.rcn.org.uk/_data/assets/pdf_file/0005/445802/Research2012Mo01.pdf. Accessed September 23, 2012.

Ders Dersi veya Ders Notları

Professor AA. Title of Lecture. [class lecture or class lecture notes]. Location: Institution; Date.

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Author or Presenter AA. Title of presentation. Presented at: Event; Month Day, Year; Location. URL. Accessed date.

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If there are six or fewer authors: Özcan NN, Özçam G, Koşar P, Özcan A, Başar H, Kaymak Ç. Correlation of computed tomography, magnetic resonance imaging and clinical out come in acute carbonmonoxide poisoning. Braz J Anesthesiol. 2016; 66(5): 529-32. doi: 10.1016/j. bjane.2014.05.006

For the book: Surname (s) and initials of the author (s), chapter title, title of the book, name of the editor (s), edition, city, publisher, year and pages.

Turkish publication: Sözen TH. Brucellosis. Topçu AW, Söyletir G, Doğanay M, editors. Infectious Diseases and Microbiology. Volume 1. Systems According to Infections. 1st Edition, Istanbul: Nobel Tıp Kitabevleri; 2002.p.636-42

For boks published in foreign languages: Philips SJ, Whistant JP. Hypertension and stroke. In: Laragh JH, Brenner BM; eds. Hypertension: Pathophysiology, diagnosis and management. 2nd ed. New York: Raven Pr;1995.p.466-78

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For boks published in foreign languages: Solcia E, Capella C, Kloppel G. Tumors of theexocrinepancreas. In: Solcia E, Capella C, Kloppel G, eds. Tumors of the Pancreas.2nd ed.Washington: ArmedForcesInstitute of Pathology. 1997.p.145-210.

For congress proceedings: Ozsoy MH, Koca G, Dincel E, et al. "Surgery and adjuvant Yttrium-90 radiosynovectomy in the treatment of diffuse pigmented villonodular synovitis (DPVNS) of the knee". 5th Meeting of the European Federation of Associations of Orthopaedic Sports Traumatology (EFOST); 67pp, November 26-30, 2008, Antalya, Turkey

For Theses: Karaca G. The Effects of These Tools on Anastomotic Health and Healing in Colon Anastomoses After Resection Using Harmonic Scalpel, Scalpel and Monopolar Electrocautery. T.C. Sağlık Bakanlığı Ankara Eğitim ve Araştırma Hastanesi, Tıpta Uzmanlık Tezi, Ankara, Turkey, 2010.

For articles published electronically: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm. Accessed September 25, 2018.

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